UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: March 25, 2016

SUBJECT: **Aldicarb:** Draft Human Health Risk Assessment in Support of Registration Review.

PC Code: 098301
Decision No.: 498310
Petition No.: NA
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: 43852501

DP Barcode: 424564
Registration No.: 48210-1
Regulatory Action: Registration Review
Case No.: 7016

CAS No.: 116-06-3
40 CFR: 180.269

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1.0 Executive Summary

This assessment has been conducted to address the requirement for a Draft Risk Assessment (DRA) to support Registration Review. As part of Registration Review, the Pesticide Re-evaluation Division (PRD) of Office of Pesticide Programs (OPP) has requested that Health Effects Division (HED) evaluate the hazard and exposure data and conduct dietary and occupational/residential exposure assessments, as needed, to estimate the risk to human health that will result from the currently registered uses of aldicarb.

Background

Aldicarb [*2-methyl-2-(methylthio)propanal O-[(methylamino)carbonyl]oxime*] is a carbamate insecticide that is marketed only as a granular product (with either low-dust corn cob grit or vinyl-coated gypsum-based substrates) with a concentration of 15% active ingredient. Aldicarb is used to control soil borne pests including mites, various insects, and nematodes on dry beans, sugar beets, cotton, peanut, sweet potato, and soybean. Applications can only be made using typical ground equipment followed by immediate soil incorporation. It is classified as a Restricted Use Pesticide (RUP) and may be purchased and used only by certified applicators or persons under their direct supervision. There are no residential uses of aldicarb, and no non-occupational exposure to aldicarb *via* spray drift is anticipated. Exposures may occur through food or drinking water as a result of crop treatments. Occupational applicators may be exposed while handling the pesticide prior to or during application. Since aldicarb is applied to crops *via* soil incorporation (generally pre-plant soil incorporation although some crop applications are allowed as a split application at plant and/or post-emergence), occupational post-application exposure is not anticipated.

The available product label indicates that the product can be used generally once or twice per growing season (pre-plant only or pre-plant plus early post-emergence), depending on the pest to be treated. The intended pests for the maximum application rates are generally nematodes, and the lesser rates for mites, thrips, Mexican bean beetles, and other pests.

Hazard Assessment

Aldicarb is a member of the *N*-methyl carbamate (NMC) class of pesticides. Like other NMCs, the initiating event in the adverse outcome pathway (AOP)/mode of action (MOA) for aldicarb involves inhibition of the enzyme acetylcholinesterase (AChE) *via* carbamylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. For aldicarb, acetylcholinesterase inhibition (AChEI) is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. Cholinesterase inhibition is the focus of this hazard characterization; the availability of reliable AChEI dose-response data is one of the key determinants in evaluating the toxicology database.

The toxicology database is complete for human health risk assessment purposes. Appropriate database uncertainty factors are applied to account for the sensitivity seen in pups in the comparative cholinesterase assay (CCA), and the Food Quality Protection Act (FQPA) factor

was reduced from 10x to 4.8x based on the weight of evidence in the toxicity database. Section 4.4 addresses the appropriate FQPA factor for aldicarb.

Aldicarb has quality dose-response data across multiple lifestages and durations *via* the oral route for both red blood cell (RBC) and brain AChEI. For aldicarb, AChEI is the most sensitive endpoint and that inhibition ultimately leads to neurotoxicity in the central and/or peripheral nervous system.

RBC AChE is the more sensitive compartment for aldicarb following oral exposure, although there are no acceptable data following dermal exposure and there is no available inhalation toxicity study for aldicarb. However, the Hazard and Science Policy Council (HASPOC) has recommended a study wavier for inhalation toxicity (TXR# 0057355, dated March 1, 2016). The available AChEI data across multiple lifestages demonstrate that the postnatal day (PND) 11 rat pups were more susceptible than adults. The results of the available acute oral human study[1] suggest a two-fold difference in toxic responses between animals and humans, with humans being the most sensitive species. Aldicarb treatment of both males and females resulted in statistically significant inhibition of both RBC and plasma cholinesterases at the two common dose levels.

Aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in rats and mice studies and the absence of a mutagenicity concern. A quantitative cancer risk assessment is not required. In acute oral lethality studies, aldicarb is classified as Toxicity Category I. There was no corneal or dermal irritation at fatal toxicity levels for the test animals. Immunotoxicity was not observed in the available toxicity data.

Endpoints and Uncertainty Factors for Risk Assessment: The endpoint for all exposure scenarios is RBC AChEI and points of departure (PODs) were selected from a human oral study. A POD for the acute dietary (all populations) exposure scenario was 0.013 mg/kg/day; no POD was selected for chronic dietary exposure because the magnitude of AChEI does not increase with continued exposure, due to the reversibility of AChEI (< 24 hours). There are no chronic toxic effects more sensitive than AChEI. The POD selected for the dermal and inhalation worker scenarios was also 0.013 mg/kg/day based on the same study.

In all exposure scenarios, interspecies (1X) and intraspecies (10X) uncertainty factors were applied since the endpoint selection is based on a human study. As a result, a total uncertainty factor of 10X was applied for all occupational exposure scenarios. Occupational risk estimates for the dermal and inhalation routes of exposure were combined since the level of concern (LOC) values are the same (LOC of 10 for both routes).

For non-occupational (dietary) exposures, an FQPA safety factor (4.8X) has also been retained for all populations including infants and children to account for the sensitivity observed between adult and young animals in the CCA.

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[1] This human study was reviewed by the Human Studies Review Board (HSRB), who concluded that use of the human study endpoint was appropriate for human health risk assessment.

Dietary (Food and Water) Exposure and Risk

Highly refined acute dietary exposure assessments incorporated U.S. Department of Agriculture's (USDA's) Pesticide Data Program (PDP) monitoring data for aldicarb and its metabolites aldicarb sulfoxide and aldicarb sulfone[2], field trial data and tolerance level residues for commodities without PDP data, empirical processing factors and default Dietary Exposure Evaluation Model (DEEM) processing factors in cases where empirical data are not available, and percent crop treated (CT) estimates. All the commodities that have tolerances for aldicarb established in the 40 CFR § 180.269 were included. The assessment was refined by using only detectable residues from imported potatoes. This refinement was possible because aldicarb is not registered in the U.S. for use on potatoes. The Environmental Fate and Effects Division (EFED) provided daily time series outputs, based on modeling, for the surface water scenario that provided the highest (MN sugar beets) and lowest (CA cotton) estimated drinking water concentrations (EDWCs). Acute assessments were conducted for food only, drinking water only, and food and drinking water combined. The drinking water assessments incorporated an estimated half-life for RBC AChEI of two hours, which is based on data of aldicarb from rats and human subjects[3]. HED also refined the acute dietary risk from food and drinking water and factored in the AChEI half-life related to aldicarb exposure.

The food only dietary exposure estimates are below HED's level of concern (LOC; i.e. <100% of the acute population adjusted dose (aPAD)) at the 99.9th percentile of exposure. Aldicarb food only dietary exposure estimate is 65% of the aPAD for children 1-2 years old, the most highly exposed population subgroup, and 25% of the aPAD for the general population at the 99.9th percentile of exposure. However, the commodity specific analysis results in exposure estimates above the level of concern for children following consumption of an estimated single serving of sweet potato or potatoes. The acute dietary exposure estimates for drinking water only are above HED's LOC at the 99.9th percentile of exposure. Dietary exposure estimates for drinking water only ranged from 1,400% to 2,900%, and 150% to 340% of the aPAD at the 99.9th percentile of exposure for the general population and most population subgroups using the scenarios that resulted in the highest EDWC (MN sugar beets) and lowest EDWC (CA cotton), respectively. Similarly, the aggregate assessment for food and drinking water (MN sugar beets scenario) results in dietary exposure above HED's LOC (also ≤2,900% of the aPAD at the 99.9th percentile of exposure for all population subgroups).

Residential (Non-Occupational) Exposure and Risk

There are currently no registered residential uses of aldicarb; therefore, a quantitative residential handler and post-application assessment was not conducted.

Spray Drift

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[2] The residues of concern for tolerance enforcement and risk assessment are the combined residues of aldicarb and its two cholinesterase-inhibiting metabolites aldicarb sulfoxide and aldicarb sulfone.

[3] HED Revised Human Health Risk Assessment for the Reregistration Eligibility Decision Document (RED). DP Barcode No. D336910. F. Fort, 02/26/2007.

The aldicarb end use product is formulated as a granular and is not anticipated to result in spray drift because of how it is applied (pre-plant/post-emergent soil incorporation).

Volatilization/Residential Bystander

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The agency has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis, and the Agency will utilize this analysis during Registration Review to determine if data (i.e., flux studies) or further analysis are required for aldicarb.

Aggregate

There are no residential uses of aldicarb. Therefore, aggregate risks include only acute dietary contributions. The acute dietary risk estimates for drinking water only and food plus drinking water are of concern (2900% of the aPAD for all infants <1 years old, the most highest exposed population subgroup).

Occupational Exposure and Risk

The aldicarb product label allows for either open pour/open cab applications (with personal protective equipment (PPE)) or closed loading/closed cab applications (i.e., engineering controls). Chemical-specific handler exposure data are available in support of open pour/open cab application scenarios. HED relied on the chemical-specific data for unit exposures for open pour/open cab applications, and on surrogate data for closed loading/closed cab applications. Based on the existing use pattern, short- and intermediate-term durations of exposure are expected for occupational handlers.

For the open pour/open cab application scenarios, using chemical-specific unit exposure data and assuming use of label required PPE (i.e., a double layer of clothing and a standard filtering facepiece respirator), there are combined dermal and inhalation risk estimates of concern (i.e., margins of exposure (MOEs) are < 10) for two scenarios. Mixer/loader risk estimates are of concern for the use on sugar beets at 4.95 lb. ai/A (MOE = 4.5) and 3 lb. ai/A (MOE = 7.4). For the closed loading/closed cab application scenarios, using available surrogate unit exposure data for engineering controls, all combined dermal and inhalation risk estimates are of concern (i.e., MOEs $\leq$ 10).

Both the low-dust corn cob grit and vinyl-coated gypsum-based substrates are considered low-dust formulations relative to the available surrogate unit exposure data from PHED (which are based on a clay-based substrate granular formulation). Exposure and risk estimates for handlers using the closed loading scenarios may be considered overestimates as the PHED surrogate unit exposures are based on a clay-based substrate granular formulation which is "dustier" than low-dust formulations such as the aldicarb products (low-dust corn cob grit and vinyl-coated gypsum based substrates).

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for aldicarb at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for aldicarb.

A quantitative occupational post-application dermal assessment has not been conducted for aldicarb because aldicarb is soil incorporated and there is limited potential for worker dermal exposure to soil incorporated pesticides.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations[4]."

Human Studies Review

An intentional dosing human oral study was used for selection of points of departure in prior risk assessments. This study has been reviewed by EPA's Human Studies Review Board (HSRB), as required by EPA's Human Subjects Protections Rule (40 CFR part 26 (effective April 7, 2006)). The HSRB discussed the study extensively during a meeting held on April 2-4, 2006 and concluded that the cholinesterase data from the aldicarb human study were reliable for use in the aldicarb single chemical aggregate risk assessment. Additionally, it was concluded that there was no clear and convincing evidence of significant deficiencies in the ethical procedures that could have resulted in serious harm (based on the knowledge available at the time the study was conducted), nor that information provided to participants seriously impaired their informed consent. The final report of the HSRB is available on the Agency website[5].

The PHED has been reviewed from an ethics perspective and no issues were found which would preclude its use in the risk assessment process. The chemical-specific study (MRID 43852501) was also reviewed for ethical requirements pertaining to the usability of data and found to be acceptable for risk assessment[6]. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[7].

2.0 HED Recommendations

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[4] http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf
[5] HSRB Report: http://archive.epa.gov/hsrb/web/pdf/april2006mtgfinalreport62606-2.pdf
[6] Memo, Nako, S. 07-21-2006. *Initial Ethics Review of a Human Study to Support the Aldicarb Risk Assessment.*
[7] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

HED has examined the toxicology and residue chemistry databases for aldicarb. Pending submittal of analytical reference standards as outlined below, there are no other residue chemistry, or toxicology data deficiencies for aldicarb. The Commodity Specific Analysis (CSA) shows that exposures exceed 100% aPAD for consumption of individual-size servings of sweet potatoes and potatoes for certain infants' and childrens' subgroups. Additionally, MOEs associated with certain occupational handler scenarios are below HED's level of concern.

2.1 Data Deficiencies

860.1650 Submittal of Analytical Reference Standards

Analytical standards for aldicarb (CAS# 116-06-3) and its metabolites aldicarb sulfoxide (CAS# 1646-87-3) and aldicarb sulfone (CAS# 1646-88-4) are currently NOT available at the EPA National Pesticide Standards Repository (personal communication with Theresa Cole, 12/16/15). Fresh samples of these standards must be submitted as soon as possible. They should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of either Theresa Cole or Thuy Nygen at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

(Note that the mail will be returned if the extended zip code is not used.)

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Adequate analytical enforcement methods are available for aldicarb and its regulated metabolites. The Pesticide Analytical Method (PAM Vol. II) lists a gas-liquid chromatography method using flame photometric detection in the sulfur mode ((GLC/FPD), designated as Method II), as available for the determination of combined residues of aldicarb and its metabolites aldicarb sulfone and aldicarb sulfoxide in plant and livestock commodities. In this method, aldicarb and aldicarb sulfoxide are oxidized to aldicarb sulfone and then total residues of aldicarb sulfone are determined. Although various modifications of Method II exist, the basic method uses an acetone:water (3:1, v:v) extraction with simultaneous oxidation of aldicarb residues of concern using a peracetic acid solution. Residues of aldicarb sulfone are subsequently purified by selective elution from a Florisil column, and the total aldicarb residue is determined as aldicarb sulfone by GLC/FPD. No interference by other sulfur-containing pesticides has been observed with this method, and the method is specific for aldicarb and its regulated metabolites. The limits of detection (LOD) for the method range from 0.01-0.05 ppm.

The 10/97 Food and Drug Administration (FDA) PESTDATA database indicate that residues of aldicarb and aldicarb sulfone are completely recovered (>80%) using multiresidue method PAM Volume I Section 302 (Luke method; Protocol D) and Section 401 (method for *N*-methyl

carbamates). Residues of aldicarb sulfoxide are also completely recovered using multiresidue method Section 302 but are only partially recovered (50-80%) using Section 401.

2.2.2 Recommended Tolerances

The residue chemistry database for aldicarb supports the following changes in tolerances:

RAC	Current Tolerance (ppm)	Recommended Tolerance (ppm)	Comment
Beet, sugar, tops	1	Revoke	Not a significant livestock feed item (Table 1 Feedstuff (June 2008))
Cotton, undelinted seed	0.10	0.20	See D425180, W. Donovan, 2/18/2016
Cotton, gin byproduct	--	0.40	See D425180, W. Donovan, 2/18/2016
Pecan	0.5	1.0	Harmonizes with Codex MRL.
Sugarcane, cane	0.02	0.10	Harmonizes with Codex MRL.

2.2.3 International Harmonization

The US tolerance definition is harmonized with the maximum residue limit (MRL) definitions for Canada and Codex: the residues of concern are aldicarb, aldicarb sulfoxide, and aldicarb sulfone. A summary of the US, Canadian, and Codex MRLs is presented in Appendix C. U.S. tolerances and MRLs (Canadian and Codex) are harmonized except for citrus fruits, cotton, peanut, pecan, potatoes, sorghum, and sugarcane. Increasing the U.S. tolerances for pecan and sugarcane to 1.0 and 0.10 ppm, respectively, will result in harmonization with Codex MRLs. Differences in good agricultural practices preclude harmonization of tolerances and MRLs for the remaining crops where differences are noted.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

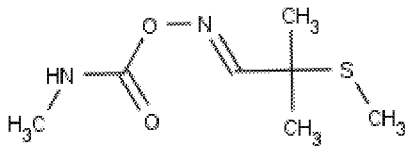
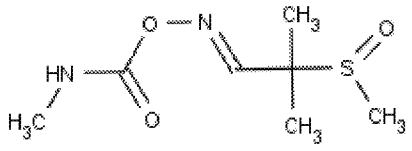
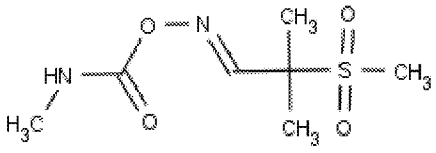
None

2.3.2 Recommendations from Occupational Assessment

No label recommendations have been identified. A summary of the occupational risk estimates have been provided, and shows that there are risk estimates of potential concern for registered uses of aldicarb based on the use information, and label-required PPE (scenarios involving PPE and engineering controls).

3.0 Introduction

3.1 Chemical Identity

Table 3.1 Chemical Structures and Nomenclature	
Common Name	Aldicarb
Chemical Structure	
Chemical name	2-methyl-2-(methylthio)propanal O-[(methylamino)carbonyl]oxime
CAS Registry Number	116-06-3
Common Name	Aldicarb sulfoxide
Chemical Structure	
Chemical name	2-methyl-2-(methylsulfinyl)propanal O-[(methylamino)carbonyl]oxime
CAS Registry Number	1646-87-3
Common Name	Aldicarb sulfone (Aldoxycarb)
Chemical Structure	
Chemical name	2-methyl-2-(methylsulfonyl)propanal O-[(methylamino)carbonyl]oxime
CAS Registry Number	1646-88-4

3.2 Physical/Chemical Characteristics

A detailed description of the physicochemical properties of aldicarb is provided in Appendix B. Technical aldicarb is a crystalline solid with a melting point of 96-97° C and a slight sulfurous odor. Crystalline aldicarb is heat-sensitive and decomposes above 100° C. Aldicarb is soluble in water (0.6%) and increasingly more soluble in the following solvents: hexane (<1%), carbon tetrachloride (4%), benzene (18%), methylethyl ketone (20%), acetone (38%), and chloroform (42%). Based on its log K_{ow} of 1.06, significant bioconcentration is not expected. Aldicarb has a relatively low vapor pressure of 0.9 mPa.

3.3 Pesticide Use Pattern

Aldicarb is a broad spectrum insecticide and is currently registered as a low-dust granular formulation (with either a corn cob substrate or a gypsum substrate) that is only applied *via* soil incorporation (EPA Reg. #87895-1). Aldicarb is registered for use on a number of agricultural crops *via* ground-based application equipment. Table 3.3.1 provides additional detail on the registered use sites.

The registered product is classified as an RUP and may be purchased and used only by certified applicators or persons under their direct supervision. As an RUP, the aldicarb product label contains substantial protective measures to prevent worker exposure. Aldicarb handlers must use

either:

- Engineering Controls (i.e., a closed loading system), or
- a minimum of coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves made of any waterproof material, and chemical-resistant footwear plus socks. In addition, during loading, equipment cleaning or repair, or spill clean-up, handlers must wear protective eyewear (goggles or face shield), a chemical-resistant apron, and a National Institute for Occupational Safety and Health (NIOSH)-approved respirator with a dust/mist filter with the MSHA/NIOSH approval number prefix TC-21C or any N, R, P or HE filter.

The available product label indicates that the product can be used generally once or twice per growing season (pre-plant or pre-plant plus early post-emergence), depending on the pest to be treated. The intended pests for the maximum application rates are generally nematodes, and the lesser rates for mites, thrips, Mexican bean beetles, and other pests.

Table 3.3.1 provides a summary of the pests and directions per use for each target crop.

Table 3.3.1. Summary of Directions for Use of Aldicarb

Applic. Timing, Type, and Equip.*	Formulation [EPA Reg. No.]	Applic. Rate (lb. ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb. ai/A)	PHI (days)	Use Directions and Limitations
Dry Bean						
Motorized Ground Equipment [nematodes]	15% ai granular 87895-1	2.1	1	2.1	90	• Apply granules in seed furrow & immediately cover with soil by mechanical means. • FOR USE ONLY IN: Colorado, Oregon, Washington, Idaho, & Michigan.
Motorized Ground Equipment [aphids]		1.05	1			
Motorized Ground Equipment [seedcorn maggot]		0.75	1			
Sugar Beets						
Motorized Ground Equipment [nematodes; pre-plant]	15% ai granular 87895-1	4.95	1 at planting application & 2 post-emergence applications per crop per year.	4.2 in California 4.95 in other states	90	• Apply granules in a 4 to 6" band & immediately cover w/ soil by mechanical means. • Plant seed into or above treated zone; • FOR USE ONLY IN: California, Colorado, Idaho, Montana, Nebraska, Oregon, Washington, & Wyoming.

Motorized Ground Equipment [leafminers/leaf hoppers]		3				• Drill granules 1 to 3" below seedline. Granules can be placed in seed furrow if rate does not exceed 1.05 lb. ai/A.
Motorized Ground Equipment [aphids]		2.1				
Cotton						
Motorized Ground Equipment [nematodes]	15% ai granular 87895-1	1.05	1 (at-plant) 1 (post-emergence)	3.15	90	• Max single application rate. • Apply granules in the seed furrow & immediately cover with soil by mechanical means.
Motorized Ground Equipment [aphids/thrips]		0.75			90	• Apply granules in the seed furrow & immediately cover with soil by mechanical means.
Motorized Ground Equipment [side dress applications]		2.1			90	• Max single rate for side dress applications. • Apply granules in the seed furrow & immediately cover with soil by mechanical means.
Peanut						
Motorized Ground Equipment [nematodes /post-pegging]	15% ai granular 87895-1	1.5	(post-emergent rate; split application)	2.55	90	• Do not make more than one application per crop per year in states other than Alabama, Florida, Georgia, North Carolina, Oklahoma, Texas, & Virginia. • Apply granules in seed furrow & immediately cover w/ soil by mechanical means. • Post-emergence applications are permitted only in fields where overhead irrigation is available.
Motorized Ground Equipment [nematodes /thrips]		1.05	At-planting			• Do not make more than one application per crop per year in states other than Alabama, Florida, Georgia, North

						Carolina, Oklahoma, Texas, & Virginia. • Apply granules in seed furrow & immediately cover w/ soil by mechanical means.
Sweet Potato						
Motorized Ground Equipment [nematodes /high rate]	15% ai granular 87895-1	3	Pre-plant or at-plant	3	120	• For use only in Louisiana & Mississippi. • Apply granules in a 12" band over open furrow or soil surface & cover immediately during bed forming by mechanically hilling up 8 to 10".
Motorized Ground Equipment [nematodes /lower rate]		1.5				
Soybean						
Motorized Ground Equipment [Mexican bean beetle /thrips]	15% ai granular 87895-1	1.05	1 application /per crop /per year	1.05	90	• FOR USE ONLY IN: Georgia, North Carolina, South Carolina, & Virginia. • Apply granules in seed furrow & immediately cover with soil by mechanical means.
Motorized Ground Equipment [nematodes /thrips]		0.75		0.75		

3.4 Anticipated Exposure Pathways

Humans may be exposed to aldicarb in food and drinking water, since aldicarb may be applied directly to growing crops and application may result in aldicarb reaching surface and ground water sources of drinking water. There are no residential uses of aldicarb; and no non-occupational exposure to aldicarb *via* spray drift is anticipated.

In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. Since aldicarb is applied to crops preplant or preemergence, occupational post-application exposure is not anticipated from those registered uses.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations[8]." As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to

[8] Available: http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf

population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups, and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures are evaluated, based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Aldicarb is a member of the *N*-methyl carbamate (NMC) class of pesticides. Like other NMCs, the initiating event in the adverse outcome pathway (AOP)/mode of action (MOA) for aldicarb involves inhibition of the enzyme acetylcholinesterase *via* carbamylation of the serine hydroxyl group located in the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). This MOA is similar to the organophosphate (OP) class of chemicals, as they both result in inhibition of the acetylcholinesterase enzyme. However, they are differentiated by their action upon the active site of the enzyme, which results in clear differences in the timing and duration of inhibition between the two classes.

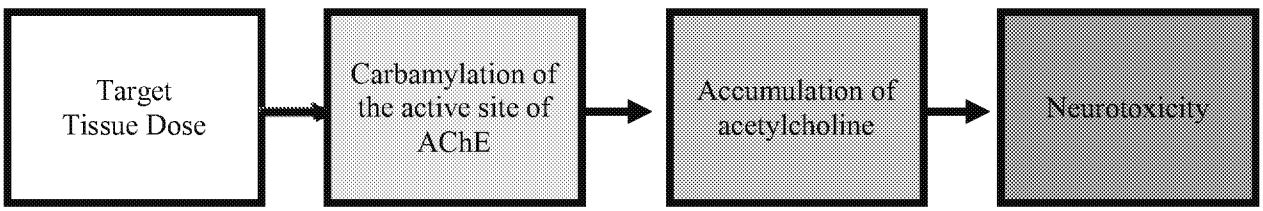


Figure 1. Adverse outcome pathway for NMCs

In the OP MOA, inhibition of acetylcholinesterase occurs *via* phosphorylation, as opposed to carbamylation with NMCs. Phosphorylation results in an irreversible binding and a permanent inhibition of the bound enzyme. Inhibition occurs within a few hours and continues until new, uninhibited enzymes are produced. This results in the OPs exhibiting a phenomenon known as steady-state cholinesterase inhibition. After repeated dosing with an OP at the same dose level, the degree of cholinesterase inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChEI at a given dose remains consistent across duration. Therefore, acute and steady state exposure durations are of concern for OPs.

The NMCs react differently in that carbamylation of the serine hydroxyl group results in a reversible binding process thus allowing for rapid reactivation of the enzyme. The NMCs, therefore, have a unique mode of action that results in rapid onset and recovery of the enzyme.

The time to peak inhibition for NMCs is typically between 15 to 45 minutes while complete recovery of the enzyme is achieved within minutes to hours (USEPA 2007 Revised NMC Cumulative Risk Assessment). Therefore, for NMCs, repeated daily exposure does not result in an increased inhibition of AChE since enzyme recovery is complete before the next acute exposure, and only acute exposure durations are of concern for NMCs, including aldicarb.

For aldicarb, AChEI is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. NMC specific cholinesterase studies are available that support aldicarb time to peak inhibition as well as recovery. Cholinesterase inhibition is the focus of this hazard characterization; the availability of reliable AChEI dose-response data is one of the key determinants in evaluating the toxicology database.

4.1 Toxicology Studies Available for Analysis

The toxicology database for aldicarb is complete, as described in 40 CFR, Part 158. No new toxicity and/or metabolism data have been received since the last risk assessment (F. Fort, 02/26/2007, D336910). HASPOC recommended waiving the acute inhalation and dermal studies (TXR# 0057355, dated March 1, 2016).

The following animal toxicology studies have been submitted in support of the registered uses of aldicarb. Additionally, there is an intentional dosing acute oral study in humans in which clinical signs and RBC cholinesterase activity were monitored.

- Subchronic oral toxicity study (dog)
- Subchronic dermal toxicity studies (rat)
- Developmental (rat and rabbit) and reproductive toxicity (rats) studies
- Comparative Cholinesterase Assay (time to peak, dose-response, and recovery)
- Chronic oral toxicity studies (rat and dog)
- Carcinogenicity studies (rat and mouse)
- Metabolism studies (rat)
- Acute and subchronic neurotoxicity studies (rat)
- Developmental neurotoxicity study (rat)
- Immunotoxicity study (mice)
- Mutagenicity battery

4.2 Absorption, Distribution, Metabolism, and Excretion (ADME)

Aldicarb is rapidly absorbed, widely distributed, and rapidly excreted, with more than 90% excreted in the urine within 24 hours after either acute or repeated oral doses. A minor part is also subject to biliary elimination and, consequently, to enterohepatic recycling. Aldicarb does not accumulate in the body. It is metabolized primarily to aldicarb sulfoxide, with a smaller amount then slowly converted to aldicarb sulfone. These three moieties (aldicarb, sulfoxide, and sulfone) may then be further metabolized to oximes and nitriles. Both the sulfoxide and the sulfone are also potent cholinesterase inhibitors. The sulfone is less toxic following an acute oral exposure than either the parent compound or the sulfoxide. The sulfoxide shows comparable acute oral toxicity to the parent, based on results of median lethal dose studies. The residues of

concern for risk assessment are the combined residues of aldicarb and its two cholinesterase-inhibiting metabolites aldicarb sulfoxide and aldicarb sulfone.

4.2.1 Dermal Absorption

There are no acceptable dermal absorption studies for aldicarb; a dermal absorption factor is needed for risk assessment since the route-specific aldicarb dermal toxicity studies in rats did not provide adequate information on the most sensitive endpoint (AChEI). Therefore, a dermal absorption factor of 100% is assumed.

4.3 Toxicological Effects

Aldicarb is an *N*-methyl carbamate pesticide that exerts its pesticidal activity and elicits adverse toxic effects by inhibition of cholinesterase activity, which has been demonstrated in whole blood, plasma, red blood cells (RBC), and brain of rats, mice, and dogs following acute, subchronic, and chronic exposure and in plasma and RBC in humans following acute oral exposure.

The time to peak AChEI as well as the recovery of RBC and brain AChE is well understood for aldicarb. In a special time to peak and recovery study, peak brain inhibition occurred within 40 minutes in adults and within 60 minutes in PND 11 pups. For RBC AChE, peak inhibition occurred within 20 minutes in adults and 40 minutes in PND 11 pups (Table 4.3.1).

Cholinesterase inhibition was also measured at several time points post exposure, thus generating an enzyme reactivation or recovery profile. In the recovery phase of the study, aldicarb had an enzyme recovery half-lives of 50-55 minutes in male pups and adults and 10 minutes in female pups. These data demonstrate that enzyme recovery is complete by the time the next exposure may occur the following day, 24 hours later. Therefore, only AChE data that is measured within minutes to an hour of the last exposure are appropriate for inclusion in the risk assessment.

Table 4.3.1. Results of BMD Modeling (mg/kg) for RBC Cholinesterase (Oral Dosing Studies)

Study	TOPE	BMD_{10}	$BMDL_{10}$
MRID 47994305[A] Acute CCA Adult Male Adult Female	20-40 minutes[B]	0.0228 0.0242	0.0153 0.0144
MRID 47994305[A] Acute CCA PND 11 Male PND 11 Female	40-60 minutes[B]	0.00477 0.00731	0.00294 0.00387
MRID 45068601[C] Acute (Moser) PND 17 PND 27 PND 67	60 minutes 60 minutes 60 minutes	0.03	0.02
MRID 43442301[D] Acute Neurotoxicity Adult	45 minutes		
MRID 43829602			

Subchronic Neurotoxicity Adult	45 minutes		
MRID 42373001 Human study Adult	60 minutes	0.02	0.01

[A]D379831, B. Sarkar, dated 7/1/2010.
[B]D380046. B. Sarkar and P. Villanueva, dated 7/14/2010.
[C]MRID 45079705.
[D]MRIDs 43442302, 43442305.

RBC and brain AChE data are available from several studies, and RBC AChE is the more sensitive compartment for aldicarb following oral exposure. Clinical signs associated with cholinesterase inhibition include tremors, salivation, lacrimation, lethargy, and prostration in rats and diarrhea and mucoid and/or soft stool in dogs. Other effects observed in rats following repeat exposure (decreased body weight and eye effects (ectopic pupil and damage to the iris)) were observed at dose levels 3-fold higher than those producing cholinesterase inhibition. Immunotoxicity was not observed. There are no acceptable data for cholinesterase inhibition following dermal exposure, and there is no inhalation toxicity study for aldicarb with which to assess cholinesterase activity.

The aldicarb database for neurotoxicity is complete, with acceptable acute, subchronic, and developmental neurotoxicity studies. Both the acute and subchronic rat neurotoxicity studies show a variety of typical clinical signs of acetylcholinesterase inhibition after oral exposures, including decreased motor activity, lacrimation, tremors, salivation, pinpoint pupils, and decreased grip strength, as well as significant decreases in RBC and brain cholinesterase activity. In the developmental neurotoxicity study in rats, AChEI and associated clinical signs, i.e., tremors, salivation, lacrimation, ataxia, miosis, and hunched posture, were observed in the dams at the same dose levels where decreased motor activity was observed in the pups in the absence of AChEI. No neuropathological effects related to exposure were seen in any of the acute, subchronic, chronic, or neurotoxicity studies.

The aldicarb database has multiple studies for informing susceptibility at different lifestages. There was no indication of increased susceptibility of fetuses in rat or rabbit developmental toxicity studies, including a rat developmental neurotoxicity study, and no increased susceptibility of the offspring in the rat reproduction study. In the developmental toxicity study in rabbits, no developmental effects were observed at any dose level, but maternal toxicity was observed, as evidenced by decreased body weight, pale kidneys, and hydroceles on the oviducts. In the developmental toxicity study in rats, the developmental effects, ecchymosis (hemorrhagic spots) of the trunk, occurred at the same dose level as the maternal effects, although the findings in the maternal rat are minimal (decreased body-weight gain and food consumption). Although cholinesterase activity was not monitored in this study, it is likely that cholinesterase inhibition occurred at all dose levels, based on the acute neurotoxicity study where RBC cholinesterase inhibition was observed following oral gavage (0.05, 0.1, and 0.5 mg/kg) at dose levels lower than the dose levels used in this developmental rat study (0.125, 0.25, and 0.5 mg/kg/day). Death and signs of cholinesterase inhibition, including hypoactivity, ataxia, tremors, lacrimation, loose feces, and cold extremities were observed in the high dose maternal rats. In the reproduction study, the effects on the offspring (reduced survival on PND 4, decreased body weight, and signs of debilitation) were observed only at the highest dose tested (1.4 mg/kg/day)

where parental toxicity also occurred, as evidenced by RBC cholinesterase inhibition and decreased body weight. In this study, the NOAEL for maternal toxicity was lower than the NOAEL for offspring toxicity.

Juvenile rat data are available for aldicarb at both the PND 11 and PND 17 lifestages. A comparative cholinesterase assay (CCA) for aldicarb provides AChE data in both the adult and the PND 11 pup to determine if the young are more sensitive than adult to aldicarb. In this study, PND 11 pups were more sensitive for both RBC (3.3-4.8X) and brain (3.7-4.5X) AChEI compared to adults. A published acute oral exposure study (Moser, 1999) demonstrated that PND 17 pups were also more sensitive (2X) than adults (brain only). In that study, decreased motor activity was observed only in the adult animals, and clinical signs of AChEI occurred more frequently in (and recovery was prolonged in) the adult compared to the PND 17 rats. The juvenile rat data available for aldicarb demonstrate that PND 11 pups are the most sensitive, as compared to PND 17 pups, as compared to adult rats.

As for the fetal lifestage, there is no indication in the toxicity database that the fetus is more sensitive than pups to aldicarb. The agency notes, however, that there is an article in the open literature (Cambon, et al., 1979) suggesting the fetus to be more susceptible than the rat dam. However, this article is not considered reliable and scientifically robust since cholinesterase inhibition in the fetus and dam was reported at time points (5 hours and 24 hours) well beyond the known time frame for cholinesterase inhibition and recovery for aldicarb and any of the NMCs.

An acute oral exposure study on aldicarb involving direct dosing of adult humans provides the timing and magnitude of plasma and RBC cholinesterase inhibition and clinical signs. Aldicarb treatment of both males and females resulted in statistically significant inhibition of both red blood cell and plasma cholinesterases at the two common dose levels. The results of the acute oral human study suggest a two-fold difference in toxic responses between animals and humans, with humans being more sensitive. This human study was reviewed by EPA's Human Studies Review Board (HSRB), as required by EPA's Human Subjects Protections rule, 40 CFR Part 26 (effective April 7, 2006), who concluded that use of the human study endpoint was appropriate for human health risk assessment. Because these human data are considered reliable, and the study is considered scientifically valid, the human study is regarded as the most suitable for this single-chemical risk assessment.

There are acceptable genotoxicity studies for all three required categories of mutagenic effects: gene mutations, chromosomal aberrations, and other genotoxic effects. The results of these studies are all negative. Aldicarb is not considered a mutagen, and it is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in studies in rats and mice.

Aldicarb is highly acutely toxic the oral, dermal, and inhalation routes of exposure in the acute lethality studies required for labeling (Toxicity Category I). It is not considered to be a dermal sensitizer; dermal and eye irritation studies were waived due to severe effects (death) following corneal and dermal dosing.

More detail concerning the characterization and quantification of the toxic effects of aldicarb is provided in Appendix A.2. OPP's cholinesterase (AChE) policy and use of BMD modeling is also described. A toxicity profile table can be found in Appendix A.2 (Table A.2.2). A table of the benchmark modeling results is provided in Appendix A.2.1 (Table A.2.3). It is noted that the toxicity profile table has been updated to include BMD results (Table A.2.2). Complete BMD modeling and data has been previously published (USEPA 2007 Revised NMC Cumulative Risk Assessment) and can be accessed as indicated within the appendix of the NMC Cumulative Risk Assessment.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

As previously described, the agency has non-guideline CCA studies in the rat that directly compare the timing and magnitude of cholinesterase inhibition in the young (PND 11) as compared to adults. The agency is also relying on RBC AChEI data from adult human subjects. Therefore, for the protection of infants and children, the agency is relying on the CCA studies to derive an aldicarb data specific FQPA Safety Factor of 4.8X (BMD adult/ BMD pup). Because of the rapid onset and recovery of the enzyme following carbamate exposure, in contrast to the irreversible binding and permanent inhibition of the bound enzyme that occurs following OP exposure, an additional safety factor is not warranted for the carbamate aldicarb.

- The toxicity database for aldicarb is complete and evaluates all relevant lifestages in the rat.
- There is no evidence of increased susceptibility or sensitivity in guideline studies in rats or rabbits to pre- and/or post-natal exposure to aldicarb.
- Developmental neurotoxicity was not observed.
- Acute, subchronic, and developmental neurotoxicity studies are available.
- Dose-response AChE data are available for comparison of inhibition between adult rats and PND 11 rat pups.
- The endpoint used for the dietary assessment is based on the species of concern (humans).
- The POD is based on the lower limit or $BMDL_{10}$ of the central estimate (BMD_{10}) for 10% cholinesterase inhibition and is health protective.
- The FQPA safety factor accounts for and is based on the sensitivity observed in the same compartment as the endpoint of concern, namely RBC cholinesterase inhibition response (endpoint of concern) between adult and young animals observed in the CCA study. See section 4.4.3 for additional detail on the sensitivity and susceptibility identified in the CCA study.

4.4.1 Completeness of the Toxicology Database

The database of toxicology studies for aldicarb is complete and includes developmental toxicity studies in the rat and rabbit, a reproductive toxicity study in the rat, acute and subchronic neurotoxicity studies in the rat, a developmental neurotoxicity study in the rat, and an acute comparative cholinesterase study in adult rats and PND 11 pups. Additionally, there are AChE data in the open literature and unpublished data that assess sensitivity of the adult rat, pregnant

rats, and the young (fetuses, PND 11, 17, and PND 27) with respect to cholinesterase inhibition and lethal doses. Immunotoxicity data are also available. Also available is an acute oral exposure study involving direct dosing of adult humans, which provides an appropriate endpoint for human health risk assessment and is regarded as the most suitable for this single-chemical risk assessment.

4.4.2 Evidence of Neurotoxicity

Aldicarb is a NMC with an established neurotoxic AOP. AChEI is the most sensitive effect in all species, routes, and lifestages and is being used in deriving the PODs.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Based on the guideline studies, there is no evidence of increased susceptibility or sensitivity in rats or rabbits to pre- and/or post-natal exposure to aldicarb. However, these studies did not include data comparing cholinesterase inhibition in young and adult animals.

In the comparative cholinesterase assay (CCA), evidence of sensitivity was observed in the young animal (PND 11) compared to the adult for both RBC and brain compartments. Additionally, there was some evidence for increased susceptibility in terms of lethal doses and brain cholinesterase inhibition in an unpublished EPA study in adult rats and PND 17 pups and PND 27 rats.

Although the cholinesterase inhibition was greater in PND 11 pups than in adults in the CCA study, the points of departure for risk assessment are health protective. The oral point of departure is based on the most sensitive compartment, RBC AChE, and based on the species of concern, namely humans. Further, an FQPA Safety Factor of 4.8X is applied, which is based on the most sensitive juvenile data (PND 11) and therefore is health protective of all lifestages.

The data-derived FQPA factor of 4.8, based on a comparison of the adult and PND 11 male RBC data (0.0228 mg/kg/0.00477mg/kg = 4.8; see table below), was selected for use in dietary risk assessment. It is noted that the RBC compartment is more sensitive than the brain compartment for both the adults and PND 11 pups. Since the point of departure for risk assessment is from an adult human RBC cholinesterase study, application of an FQPA factor based on the RBC cholinesterase rodent data is necessary to account for the additional sensitivity seen in the pups.

Table 1. FQPA Factor Estimates Based on the PND 11 CCA Study

Sex	Compartment	Adult BMD_{10} [1]	PND 11 Pups BMD_{10} [1]	FQPA Factor [2]
Male	Brain	0.0535	0.0143	3.7
	RBC	0.0228	0.00477	**4.8**
Female	Brain	0.0615	0.0136	4.5
	RBC	0.0242	0.00731	3.3

[1] BMD_{10} is defined as the estimated dose at which 10% cholinesterase inhibition would be observed.

[2] The FQPA factor is calculated by dividing the BMD_{10} for the adults by the BMD_{10} of the pups for the same sex and compartment. The FQPA factor must be derived from the same compartment as that relied upon for the point of departure, i.e. RBC.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The food exposure assessment was based on maximum percent crop treated estimates, and PDP monitoring data supplemented by field trial data, as appropriate. Water estimates were based on modeling programs designed to provide high-end water values.

4.5 Toxicology Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

There have been no changes since the last dose-response assessment and no changes to the prior recommendations for combining routes of exposure or cancer classification. Table 4.3.1 summarizes the benchmark dose analyses considered in selecting aldicarb endpoints, and Table 4.5.4.1 summarize the aldicarb toxicity endpoints, uncertainty factors, and points of departure. Detailed description of the studies used as a basis for the selected endpoints are presented in Appendix A.

As discussed previously, since peak inhibition of cholinesterase occurs rapidly (within 20-60 minutes) with recovery occurring within minutes to hours (recovery half-lives of 10-50 minutes), the daily exposure to aldicarb is the toxicological duration of concern. This is supported by the toxicity database for aldicarb, which indicates that the most sensitive toxicological effect is inhibition of AChE following acute exposure. As discussed above, the magnitude of AChEI does not increase over repeated administration. Therefore, based on this mode of action and time course for inhibition and recovery, the endpoints selected are protective for acute and repeat exposure assessment.

Consistent with risk assessments for other AChE-inhibiting compounds, OPP has used a benchmark response (BMR) level of 10% and has thus calculated BMD_{10}s and $BMDL_{10}$s. The BMD_{10} is the estimated dose where AChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}. As a matter of science policy, the agency uses the BMDL, not the BMD, for use as the POD (USEPA, 2012). All BMD/BMDL modeling was completed using USEPA BMD Software, version 2.4; an exponential model or Hill model was used to fit the data.

Acute Dietary Endpoint (All Populations)

The agency evaluated the toxicity profile for aldicarb and considered the human acute oral study to be appropriate for assessment of the acute dietary exposure and risks. A $BMDL_{10}$ POD of 0.013 mg/kg/day was selected from the acute human oral study and was associated with RBC cholinesterase inhibition. Data from the human oral study are appropriate for acute POD derivation, since effects were observed after a single exposure and the endpoint is the most sensitive adverse response in all populations (infant and children, females 13+, and adults).

An uncertainty factor of 48X (1X interspecies extrapolation, 10X for intraspecies variation, and a 4.8X for FQPA safety factor (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain an acute population adjusted dose (aPAD) of 0.00027 mg/kg/day for dietary exposure scenarios for all populations, including infants and children.

Chronic Dietary Endpoint (All Populations)
A chronic dietary assessment was not conducted since recovery data demonstrate that the rapid recovery of cholinesterase following acute exposure to aldicarb prevents cumulative toxicity; consequently, longer-term exposures are considered a series of acute exposures. A chronic assessment is, therefore, not considered appropriate for aldicarb. Aldicarb has been classified as Category E, Evidence of Non-Carcinogenicity for Humans (TXR# 012871, dated 9/15/1998); therefore, a cancer dietary assessment was not required.

Dermal Endpoint
A POD of 0.013 mg/kg/day was selected from the human acute oral study, based on RBC cholinesterase inhibition. The endpoint/POD is applicable to short- and intermediate-term dermal exposures. In the case of aldicarb, the magnitude of AChEI does not increase with continued exposure, and AChEI is generally reversible within 24 hours. As discussed in Section 4.0, acute inhibition of acetylcholinesterase is the main exposure duration of concern. Short- and intermediate-term exposures can be considered a series of acute exposures, with regard to AChEI. A total uncertainty factor of 10X is appropriate for occupational dermal exposures since exposures are expected for adults only, not children (1X for interspecies extrapolation, 10X for intraspecies variation, resulting in a LOC of 10). There are no acceptable dermal absorption studies for aldicarb. A 100% dermal absorption factor is assumed.

Inhalation Endpoints
A POD of 0.013 mg/kg/day was selected from the human acute oral study, based on RBC cholinesterase inhibition. The endpoint/POD is applicable to short- and intermediate-term inhalation exposures. A route-specific inhalation study is unavailable; however, HASPOC recommended that the acute inhalation study be waived (TXR# 0057355, dated March 1, 2016) based on the following: (1) aldicarb is a Restricted Use Pesticide and exposure to aldicarb is to granules, which are soil-incorporated; (2) humans are 2X more sensitive to aldicarb than rats; (3) the POD is based on human (oral) data; (4) the acute rat inhalation study does not involve a detailed toxicological examination of the respiratory system; (5) aldicarb is extremely toxic *via* the oral, dermal, and inhalation routes (Toxicity Category 1); (6) based on a comparison of doses (oral vs. inhalation) that result in 50% deaths (on a mg/kg basis), the oral and inhalation doses in the rat are similar and likely the result of cholinesterase inhibition. An inhalation study with rats would not be expected to provide a lower point of departure than the one based on the human data. The total uncertainty factor of 10X is appropriate for occupational inhalation exposures (1X for interspecies extrapolation, 10X for intraspecies variation, resulting in a LOC of 10).

4.5.2 Recommendations for Combining Routes of Exposure for Risk Assessment

If the toxicity endpoints and PODs for dermal, oral, and inhalation routes of exposure are similar the exposure or risk estimates from these exposure routes need to be combined. In the case of aldicarb, the dermal, inhalation and oral routes are based on the same effects, and can be

combined. The dermal and inhalation routes of exposure were combined for the occupational risk assessment using the Total MOE approach. Additional detail is provided in Section 11.1.

4.5.3 Cancer Classification and Risk Assessment Recommendation

In accordance with the Agency's 2005 Guideline for Carcinogen Risk Assessment, aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for Aldicarb for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	$BMDL_{10}$ = 0.013 mg/kg	FQPA SF = 4.8X UF_H = 10 UF_A= 1x	Acute RfD = 0.0013 mg/kg/day aPAD = 0.00027 mg/kg/day	Human oral study MRIDs 43829602, 45068601, 43442302, 43442305, 42373001 BMD_{10} = 0.02 mg/kg, based on RBC cholinesterase inhibition
Chronic Dietary (All Populations)	A quantitative chronic assessment was not conducted because the toxicity database for aldicarb indicates that the magnitude of AChEI does not increase with continued exposure, due to the reversibility of AChEI (< 24 hours). There are no chronic toxic effects more sensitive than AChEI.			
Cancer (oral, dermal, inhalation)	Classification: Aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern.			

AChEI = acetylcholinesterase inhibition. Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). BMD_{10} = Benchmark Dose; dose that corresponds to 10% response in AChEI. $BMDL_{10}$ = Benchmark Dose estimate based on the lower 95% confidence interval where 10% AChEI would be observed. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose. a = acute. RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

Table 4.5.4.2 Summary of Toxicological Doses and Endpoints for Aldicarb for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Exposures (Short- and Intermediate-Term)	$BMDL_{10}$ = 0.013 mg/kg DAF = 100%	UF_A=1x UF_H=10x	Occupational LOC for MOE = 10	Human oral study MRIDs 43829602, 45068601, 43442302, 43442305, 42373001 BMD_{10} = 0.02 mg/kg, based on RBC cholinesterase inhibition

Table 4.5.4.2 Summary of Toxicological Doses and Endpoints for Aldicarb for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation Exposures (Short- and Intermediate-Term)	$BMDL_{10}$ = 0.013 mg/kg	UF_A=1x UF_H=10x	Occupational LOC for MOE = 10	Human oral study MRIDs 43829602, 45068601, 43442302, 43442305, 42373001 BMD_{10} = 0.02 mg/kg, based on RBC cholinesterase inhibition
Cancer (oral, dermal, inhalation)	Classification: Aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern.			

DAF = dermal absorption factor. Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). BMD_{10} = Benchmark Dose; dose that corresponds to 10% response in AChEI. $BMDL_{10}$ = Benchmark Dose estimate based on the lower 95% confidence interval where 10% AChEI would be observed. MOE = margin of exposure. LOC = level of concern.

4.6 Endocrine Disruption

As required by Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and Federal Food, Drug and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of the reregistration decision for aldicarb, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), aldicarb is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between

October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[9] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website[10].

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

Adequate plant and animal metabolism studies are available for aldicarb and these have been reviewed in detail elsewhere (F. Fort, 2/26/2007, D336910). Residues of concern include parent aldicarb and the cholinesterase inhibiting metabolites aldicarb sulfoxide and aldicarb sulfone.

5.1.2 Summary of Environmental Degradation

Aldicarb degrades to aldicarb sulfone and aldicarb sulfoxide, primarily by aerobic soil metabolism (parent half-lives range from 1 to 28 days in a variety of soils). Aerobic soil metabolism half-lives for the combined residues (i.e., aldicarb, sulfoxide, sulfone) range from 11 to 136 days, with a 90th percentile upper bound on the mean of 55 days. Aldicarb is relatively stable to hydrolysis and slowly hydrolyzes at pH 9 (MRID 00102065). Aldicarb sulfoxide hydrolyzes more quickly ($t_{1/2}$ = 2 - 3 days) at pH 9 than at pH 7 (about 6% at 28 days) (MRID 00102066). Aqueous photolysis rapidly degrades aldicarb to oxime and nitrile forms (i.e. with a $t_{1/2}$ of 4 days: MRID 42498201). However, this process will only be dominant in clear, shallow waters, and will not affect residues in the subsurface.

Aldicarb and its degradates are considered highly mobile in soil. The aldicarb fate database indicates that the total toxic residues of aldicarb will degrade slowly in upper soil layer, move fairly rapidly into the subsurface (the rate of movement depending upon the permeability of the soil and amount of excess water that moves through the soil), and potentially persist in the subsurface and ground water under acidic (pH<7) conditions. The sulfoxide and sulfone degradates will hydrolyze rapidly in alkaline soils, so the ultimate fate in ground water will depend upon the pH of the soil, vadose zone, and aquifer.

5.1.3 Comparison of Metabolic Pathways

In rats, is rapidly absorbed, widely distributed, and rapidly eliminated. In rats, livestock, plants, and in the environment, aldicarb is rapidly metabolized to aldicarb sulfoxide, then slowly converted to aldicarb sulfone. These three moieties (aldicarb, sulfoxide, and sulfone) may then

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[9] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals

[10] http://www.epa.gov/endo/

be further metabolized to oximes and nitriles. Both the sulfoxide and sulfone are also potent cholinesterase inhibitors. The sulfone is less toxic following an acute oral exposure than either the parent compound or the sulfoxide, which show comparable acute oral toxicity. Aldicarb and its two cholinesterase-inhibiting metabolites are the residues of concern for risk assessment for all routes of exposure and for tolerance reassessment (see Table 5.1.4).

5.1.4 Residues of Concern Summary

Table 5.1.4 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix	Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Aldicarb, aldicarb sulfoxide, and aldicarb sulfone	Aldicarb, aldicarb sulfoxide, and aldicarb sulfone
Livestock		
Drinking Water		Not Applicable

5.2 Food Residue Profile

Adequate residue chemistry data are available to support the current tolerances for aldicarb.

Crop Field Trials: Cotton and sorghum field trial studies were called-in as a result of reregistration along with a supporting storage stability study in a July 2008 Generic Data Call-In (GDCI-098301-27347). The registrant agreed to cancel the use on sorghum, which was announced in a Federal Register notice dated October 8, 2008 (Volume 73, Number 196, pp. 58958-58962). Therefore, the data on sorghum are no longer required. The registrant has submitted the required cotton field trial studies, and these data are acceptable (W. Donovan, 02/18/2016, D425180). No further crop field trial data are required.

Meat, Milk, Poultry, and Eggs (MMPE): The most recent evaluation of aldicarb residues in MMPE commodities was provided in a GDCI review (W. Donovan, 02/18/2016, D425180), where HED concluded that residues in livestock commodities are classified under 40 CFR §180.6(a)(3), i.e., there is no reasonable expectation of finite residues.

5.3 Water Residue Profile

Drinking water residue estimates were provided by EFED (E. Wong, 6/17/2015, D427697) who estimated drinking water concentrations (EDWCs) for the total toxic residues (TTR) including aldicarb and two structurally similar degradates, aldicarb sulfoxide and aldicarb sulfone. Tier II surface water EDWCs were estimated with the Surface Water Concentration Calculator (SWCC). The Pesticide Root Zone Model-Groundwater (PRZM-GW) was used to estimate groundwater EDWCs at pH 6. TTR degradation varies with pH; slight acidic conditions yielded

the highest concentration of aldicarb TTR in groundwater. Available monitoring data were evaluated and determined not to be appropriate for use in quantitative dietary modeling.

The groundwater EDWCs are less than those for surface water; therefore, EFED recommended that the EDWCs for surface water are the most appropriate values for use in dietary exposure modeling. The highest one-in-ten year peak, annual mean, and 30-year mean EDWCs (187, 16, and 5.3 µg/L, respectively) are based on the labeled use of aldicarb on sugar beets at 4.05 lb. ai/acre per year. The scenario that provided the lowest EDWC was surface water in California (CA cotton PRZM scenario) after application of the rate used for cotton (CA Cotton). Results are summarized in Table 5.3. The entire 30-year distributions of estimated daily concentrations in surface water obtained for the MN sugar beets and CA Cotton scenarios were incorporated into separate DEEM-FCID analyses and used in the acute probabilistic analyses to provide a broader estimate of total risks from drinking water under different use scenarios.

Table 5.3 Summary of Estimated Surface Water and Groundwater Concentrations for Aldicarb and its Degradates.

Scenario	MN Sugar Beets Surface Water Conc., ppb[a]	CA Cotton Surface Water Conc., ppb[a]	Groundwater Conc., ppb[b]
Acute	187	23.1	93.2
Chronic (non-cancer)	16	1.75	40
Chronic (cancer)	5.3	0.45	40

[a] From SWCC: Sugar beets or cotton.

[b] From PRZM-GW (pH 6): Sugar beets.

E. Wong, 6/17/15, D427697: Application rates are different for both surface and ground water modeling because application instructions on the label specified that the 4.95 lb. ai/A rate is covered with soil, thus minimizing surface runoff exposure, while 4.05 lb. ai/A is the highest application rate that can be applied over irrigation furrow without soil cover, which increases potential surface water exposure.

Summary of Water Monitoring: Aldicarb, aldicarb sulfoxide, and aldicarb sulfone were monitored in non-targeted sites for surface and groundwater in all 50 states in the U.S. including the District of Columbia from February 1986 to December 2014. Note that much of this monitoring data was collected prior to mitigation and use reduction associated with reregistration of aldicarb. The mitigation was implemented in 2009.

Concentrations of aldicarb detected in surface water were higher than those in groundwater and inversely, its sulfoxide and sulfone were higher in groundwater than in surface water. The highest detections of aldicarb residues of concern in these databases are 5.4 ppb in surface water (parent aldicarb) and 9.0 ppb in ground water (sulfone).

5.4 Dietary Risk Assessment

5.4.1 Overview of Residue Data Used

Tolerances are established in the 40 CFR § 180.269 for aldicarb in support of domestic and foreign uses. The tolerances for dry bean, sugar beets, cotton, peanut, soybean and sweet potato are based on domestic uses of aldicarb. Although tolerances for potato, citrus, coffee, pecan, sorghum and sugar cane are established in the CFR, there are no registered uses in the U.S.A. USDA PDP monitoring data for potato, sweet potato, and orange (translated to other citrus commodities) were incorporated in the dietary assessment. Residues of parent aldicarb, aldicarb sulfone, and aldicarb sulfoxide were combined using the PDP sample identification number. When one of the residues of concern was not detectable in the sample, ½LOD values were used. Field trial data provided in a previous dietary assessment (C. Olinger, 08/16/2010, D299883) were used for soybean, dry beans, pecan, cottonseed, coffee and peanut. The existing tolerance for grain sorghum was used in the assessment. Sugar beets and sugarcane were excluded from the assessments, since aldicarb residues would not be expected in the processed commodities as consumed (sugar processing procedures result in no aldicarb residues).

Empirical processing factors (PFs) for aldicarb in cooked potato food forms (0.62 for fried; 0.5 for boiled), dry beans (0.05 for baked, boiled, fried, canned:cooked, canned:boiled, cooked:no food form specified), soybean oil (0.3), peanut oil (0.18), and cottonseed oil (0.1) were incorporated in the assessment. The processing/cooking studies indicate a general reduction of residues; since residues are systemic, the reduction in residues is not related to removal of certain inedible commodity fractions, e.g., peel. Moreover, DEEM default processing factors of 6.5 for dry potato and 1 for the remaining processed commodities were used.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The Biological Economic Analysis Division (BEAD) provided percent of crop treated estimates for the years 2004 to 2012. The following maximum percent crop treated estimates (Updated Screening Level Usage Analysis Report for Aldicarb, 12/18/2014, PC Code 098301) were used in the acute dietary risk assessment for the following crops that are currently registered for aldicarb: cotton: 35%; dry beans: 2.5%; peanuts: 45%; soybeans: 2.5%; and sugar beets: 10%. 100% of crop treated was assumed for sweet potato. Percent of crop treated estimates were provided for grapefruit, oranges, lemon, pecans, potato, sorghum, and sugarcane; however, these were not used as these crops do not have uses registered in the U.S.A. BEAD provided information on the percent of imported commodities for which data were available from 2009-2013[11]. The percent of imports were included for the following crops: grapefruit: 2%; lemons: 10%; orange: 8%; pecans: 58%; fresh potato: 8%; frozen potato: 21%; and 100% was assumed for limes and coffee. The assessment assumes that all of the imported commodities have been treated with aldicarb.

5.4.3 Acute Dietary Risk Assessment

Highly refined acute assessments were conducted for food only, drinking water only and food plus drinking water (Tables 5.4.6.1 and 5.4.6.2) (refer to D430197). These assessments incorporated an estimated half-life for RBC AChEI of two hours which is based on data from rats and human subjects. HED also refined the acute dietary risk from food and drinking water by incorporating the time and amounts consumed for each eating occasion instead of total daily

[11] Personal Communication from EFED (e-mail from Donald Atwood); 11/25/2015

intake. This is then used to estimate exposures and risks on each eating occasion throughout the day and factoring in the AChEI half-life related to aldicarb exposure. Moreover, PDP for imported potatoes only were used; residues from domestic potato samples were not included in the analysis since use on potatoes is no longer registered in the U.S.

The acute dietary exposure estimates from food alone are below HED's level of concern (i.e. <100% aPAD) at the 99.9th percentile of exposure after refinement. The acute dietary exposure is 25% of the aPAD for the general population, and 65% of the aPAD for children 1-2 years old, the highest exposed population subgroup.

The acute dietary exposure estimates from drinking water alone are above HED's level of concern (i.e. >100% of the aPAD) at the 99.9th percentile of exposure. Dietary exposure estimates for drinking water ranged from 1,400% to 2,900%, and 150% to 340% of the aPAD at the 99.9th percentile of exposure for the general population and most population subgroups using the scenarios that resulted in the highest EDWC (MN sugar beets) and lowest EDWC (CA Cotton), respectively.

Similarly, for food plus drinking water (MN sugar beets), the dietary exposure is above HED's LOC, ranging from 1,400% to 2,900% aPAD at the 99.9th percentile of exposure for all population subgroups. These results indicate that drinking water is the main contributor to the dietary exposure.

5.4.4 Chronic Dietary Risk Assessment

A chronic assessment was not conducted because the toxicity database for aldicarb indicates that AChEI is the most sensitive effect found, and the magnitude of AChEI does not increase with continued exposure since AChEI is generally reversible within 24 hours at the levels relevant to the dietary risk assessment. The longer-term exposures could be considered as a series of acute exposures, with regard to AChEI. All other effects noted in the sub-chronic and chronic toxicity studies were observed at higher doses.

5.4.5 Cancer Dietary Risk Assessment

A cancer dietary exposure and risk assessment was not conducted since aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans

5.4.6. Dietary Assessment Summary Tables

The results of the acute dietary exposure analyses are reported in Table 5.4.6.1 for food only considering all commodities that have tolerances (domestic and import), and in Table 5.4.6.2 for food and drinking water.

Table 5.4.6.1. Summary of Acute Dietary (Food Only) Exposure and Risk for Aldicarb at the 99.9th Percentile of Exposure Considering All Commodities with Tolerances		
Population Subgroup	All Commodities	
	Dietary Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.000067	25
All Infants (<1 year old)	0.000089	33
Children 1-2 years old*	**0.000177**	**65**
Children 3-5 years old	0.000133	49
Children 6-12 years old	0.000076	28
Youth 13-19 years old	0.000050	18
Adults 20-49 years old	0.000044	16
Adults 50-99 years old	0.000049	18
Females 13-49 years old	0.000046	17

* The population with the highest risk estimate is in bold.

Table 5.4.6.2. Summary of Acute Dietary (Drinking Water Only and Food plus Drinking Water) Exposure and Risk for Aldicarb at the 99.9th Percentile of Exposure						
Population Subgroup	Water Only for CA Cotton Scenario		Water Only for MN Sugar Beets Scenario		Food plus Water for MN Sugar Beets Scenario	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.000492	180	0.004616	1700	0.004607	1700
All Infants (<1 year old)*	0.000909	**340**	0.007775	**2900**	0.007723	**2900**
Children 1-2 years old	0.000743	280	0.006928	2600	0.006976	2600
Children 3-5 years old	0.000628	230	0.005760	2100	0.005750	2100
Children 6-12 years old	0.000446	170	0.004206	1600	0.004220	1600
Youth 13-19 years old	0.000396	150	0.003696	1400	0.003664	1400
Adults 20-49 years old	0.000501	190	0.004677	1700	0.004672	1700
Adults 50-99 years old	0.000448	170	0.004186	1600	0.004155	1500
Females 13-49 years old	0.000498	180	0.004688	1700	0.004677	1700

* The population with the highest risk estimate is in bold.

5.4.7. Commodity Specific Analysis

Commodity specific analysis (CSA) was conducted for aldicarb to obtain estimates of the acute exposure and risk following a single consumption event for potatoes and for sweet potatoes. Dietary exposures were calculated using typical serving sizes for amounts consumed and USDA PDP monitoring data. While aldicarb is no longer used domestically on potatoes, tolerances remain in place which allows import into the U.S. of potatoes containing aldicarb residues. Dietary exposures were expressed as a percent of the acute population adjusted dose (0.00027 mg/kg/day).

Table E.2 summarizes the commodity specific analysis for aldicarb. The highest %aPAD were for pre-school age children eating the equivalent of one average size potato (130% aPAD) or sweet potato (300% aPAD). This CSA is considered a highly refined assessment for the following reasons:

- The aPAD was calculated using:
    - an endpoint/NOAEL from a human study (the inter-species factor was reduced to 1X),
    - a 4.8X **data-derived** factor for children, and
    - a 10X intra-species factor;
- PDP data were used to estimate residues, and processing/cooking data was considered, as appropriate.

A cooking factor of 1x was applied based on empirical data. Although processing factors of 0.5 (boiled, canned:cooked, canned:boiled) and 0.62 (fried) are available for sweet potato or potato, these do not apply to cooked baked sweet potato. Also, because aldicarb is applied as a soil-incorporated, granular formulation, residues may be significantly higher in individual potatoes or sweet potatoes relative to residues measured in the PDP samples, which are composites of many individual potatoes, i.e., the composite samples represent an average residue in all of the potatoes in the analyzed sample, whereas all of the residue may actually be present in only a subset of the individual potatoes. In fact, limited residue data available indicate that residues of aldicarb and its metabolites in the individual samples could be at least 2.4 times that of the composite sample suggesting that the CSA risk estimates may underestimate actual risks from consumption of individual potatoes or sweet potatoes.

For these reasons, the conservative inputs used to estimate the aldicarb CSA risks should be considered marginal, with risk estimates closely approximating actual potential risks to the small portion of the U.S. population consuming commodities containing residues at these levels.

Sweet Potato

The PDP monitoring data (2008-2010) for sweet potatoes show two detects, 0.07784 ppm and 0.06894 ppm of 1476 samples of unpeeled sweet potato, that are above the threshold (i.e. residue level that would result in risk at the level of concern) for preschoolers (0.026 ppm). PDP monitoring data is available for sweet potato baby food which showed no detects above the limit of detection of 0.0083 ppm. This results in exposures below the level of concern for infants, 24% of the aPAD. The dietary exposure is above HED's level of concern (i.e. >100% of the aPAD) for preschoolers consuming one medium size sweet potato (157 g); exposure is 300% of the aPAD. Exposures are below the level of concern for adults consuming one medium size sweet potato (75% of the aPAD).

Potato

PDP monitoring data for imported potatoes were used in the CSA; domestically cultivated potato data from 2006-2009 PDP monitoring were excluded since aldicarb is not registered for use in the U.S. as part of the 2010 mitigation. PDP monitoring data generated after cancelation of the U.S.A. use on potato is not available at this time. The dietary exposure do not exceed the level of concern for infants (100% of the aPAD) consuming ½ medium size potato (71 g), is above HED's level of concern for preschoolers (130% of the aPAD) consuming one medium size sweet

potato (142 g), and is below the level of concern for adults consuming 1 medium size potato (33% of the aPAD).

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

6.1 Residential Handler Exposure

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. There are currently no registered or proposed residential uses for aldicarb; therefore, a residential handler assessment was not performed.

6.2 Residential Post-Application Exposure

There are currently no registered or proposed residential uses for aldicarb; therefore, a residential post-application assessment was not performed.

7.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. Where appropriate, the potential for spray drift will be quantitatively evaluated for each pesticide during the Registration Review process which ensures that all uses for that pesticide will be considered concurrently. However, the aldicarb end use product is formulated as a granular and will not result in spray drift because of how it is applied (pre-plant/post-emergent soil incorporation).

8.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

There is an available air monitoring study conducted in California by the California Air Resources Board (CARB)[12]. The report presents the results of application air monitoring (in Fresno County) and ambient air monitoring (in Fresno and Kern Counties).

Application site air monitoring (i.e., also known as field volatility) refers to the collection of air samples around the edges of a treated field during and after a pesticide application. Samples are generally collected for short intervals (e.g., < 8 hours), for at least the first day or two after application with subsequent samples increasing in duration. In this type of study, it is typically known when an application occurred, the equipment used for the application, and the application rate. Application site monitoring data represents an exposure to vapors at or near the field edge resulting from an application.

Ambient air monitoring typically is focused on characterizing the airborne pesticide levels within a localized airshed or community structure of some definition (e.g., city, township, or municipality). This type of monitoring effort also can be focused on capturing chronic background levels or other temporal characteristics of interest such as focusing on seasonal

[12] *Report for the Application and Ambient Air Monitoring of Aldicarb.* California Environmental Protection Agency Air Resources Board. November 16, 1998. http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacpdfs/aldicarb.pdf

pesticide use patterns. Typically, samples are generally taken for 24 consecutive hours and collected at the same site over an extended period of time (e.g., several weeks or months). In contrast to application site air monitoring, information on the precise timing and location of pesticide applications are rarely collected in ambient air monitoring studies. However, this does not mean that an application did not occur near an ambient sampler during the monitoring period.

Two application studies were conducted in Fresno County; however, due to problems with the first study, which was associated with cotton planting, a second study was conducted which was associated with cotton "at first squaring". First squaring refers to a process of manual weed control (tilling) during which the insecticide is applied to the cotton row berms. Of the twenty application samples collected during the first study, two were found to be detected (meaning results were below the limit of quantitation but equal to or above the LOD) and the remaining 18 were less than the LOD of 0.050 µg/sample. For the second application study, all four background samples had results less than the LOD. Of the twenty-four application samples collected, all were found to be less than the LOD of 0.050 µg/sample.

Ambient monitoring was initially conducted during a three week period from March 24 to April 11, 1997 in Fresno County. The monitoring was scheduled to coincide with cotton planting and the aldicarb samplers were collocated with samplers being used for an ambient phorate air monitoring study. No detectable levels of aldicarb were observed during the first three weeks of monitoring in Fresno County, therefore, the remaining three weeks of monitoring was conducted in June in Kern County. Of the 60 ambient samples collected in Fresno County and the 55 collected in Kern County, all were found to be less than the LOD of 0.050 µg/sample.

9.0 Aggregate Exposure/Risk Characterization

The registered aldicarb uses are not anticipated to result in residential exposure, and thus the acute dietary (food and drinking water) exposure estimates provided in Table 5.4.6.2 represent the acute aggregate exposure.

10.0 Cumulative Exposure/Risk Characterization

The FQPA requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. Aldicarb is a member of the *N*-methyl carbamate (NMC) common mechanism group. NMCs like aldicarb share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the NMC common mechanism grouping per OPP's *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999). The 2007 Cumulative Risk Assessment (CRA) and the subsequent revision used brain AChEI in female rats as the source of dose response data for the relative potency factors and PODs for each NMC, including aldicarb. Prior to the completion of Registration Review, OPP will update the NMC CRA to incorporate new toxicity and exposure information available since 2007.

The most recent cumulative risk assessment for the NMC carbamates was issued for comment on September 26, 2007 and is available on the Agency website[13].

Prior to a final registration review decision for aldicarb, the Agency will determine if there is any new information, such as new hazard or exposure data or information on changes to the use pattern, which would affect the cumulative risk assessment. Should the Agency determine that new information on aldicarb is available that could potentially impact the cumulative risk assessment and result in a risk of concern, the Agency will revisit the cumulative risk assessment.

11.0 Occupational Exposure/Risk Characterization

11.1 Short- and Intermediate-Term Handler Risk

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements, amount of chemical used in each application, the kinds of equipment used, the target being treated, and the level of protective gear or controls used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Loader – granules for ground application equipment ("open pour" scenario);
- Loader – granules for ground application equipment (closed loading/engineering controls (EC) scenario);
- Applicator – open cab granule application for ground application equipment; and
- Applicator – closed cab granule application for ground application equipment (EC).

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Assumptions and factors, as well as algorithms used to estimate non-cancer exposure and dose for occupational handlers are detailed in the most recent ORE memo (M. Lloyd, 3/28/16, D430949).

Exposure Duration: Based on the registered use pattern for aldicarb, short- and intermediate-term exposures are expected, and the POD selected for dermal/inhalation risk assessment is protective of both exposure durations. Long-term exposures are not anticipated. Since aldicarb toxicity does not increase with increasing duration of exposure, the short-term assessment is protective for all occupational handler exposures to aldicarb.

[13] http://itrcweb.org/FileCabinet/GetFile?fileID=6883

Personal Protective Equipment: Estimates of dermal and inhalation exposure were calculated for various levels of personal protective equipment (PPE). Results are presented for loaders and applicators based on the personal protective equipment and/or engineering controls identified on the label:

- Baseline, plus chemical-resistant gloves and coveralls with a PF5[14] respiratory protection device, or
- Engineering controls (closed loading system or closed cab).

Unit Exposures:

It is the policy of HED to use the best available data to assess handler exposure. For this assessment, two main sources of data were used:

- The first source of data was a chemical-specific study (MRID 43852501[15]) that collected occupational handler dermal and inhalation exposure data representative of the registered "low dust" formulation. Additional details on the study description and specifics of the data can be found in the ORE memo (M. Lloyd, 3/28/16, D430949). For scenarios representing open loading and open cab application of low dust corn cob granules, unit exposure data from the chemical-specific study were used. It should be noted that the study was conducted without handlers wearing a respirator; however, the currently registered label requires handlers wear a respirator. Therefore, the inhalation unit exposures were adjusted to account for current label PPE (i.e., filtering facepiece respirator; an 80% assumed reduction from the inhalation unit exposure).
- The second source of data includes generic handler data. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[16]. These data were used to assess scenarios representative of closed loading systems (engineering controls).

Combining Exposures/Risk Estimates

Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes are identical. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = Point of Departure (mg/kg/day) ÷ Combined dermal + inhalation dose (mg/kg/day) Combined dermal + inhalation dose (mg/kg/day)

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[14] A NIOSH approved particulate respirator with any R or P filter with NIOSH approval number prefix TC-84A; or a NIOSH approved powered air purifying respirator with HE filter with NIOSH approval number prefix TC-21C.

[15] EPA MRID 43852501: Rosenheck, L., Schuster, L. (1995) Worker Loader and Applicator Exposure to Temik 15G. Study number 94388, Unpublished study prepared by ABC Laboratories, Pan-Ag Division; Rhone-Poulenc Ag Company.

[16] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Occupational handler risk estimates are presented below in Table 11.1.1 and 11.1.2.

Table 11.1.1 shows loader and applicator risk estimates assuming open pour/open cab application using label-specified PPE using the available chemical-specific handler unit exposure data. Table 11.1.2 shows loader and applicator risk estimates assuming closed loading/closed cab application (i.e., engineering controls) using only PHED surrogate unit exposure data.

Where risk concerns exist, the combined risk estimates are driven by dermal exposure. It should be noted that an assumption of 100% dermal absorption was used in the dermal exposure/risk calculations since an acceptable dermal absorption study was not submitted. Given that the registered product is a granular formulation, it is unlikely that 100% absorption would occur.

The following risk estimates of concern were identified (and are noted in bold in the tables):

Open Mixing/Loading and Open-cab Application Using Label-specified PPE:

- Mixer/loader scenarios (using chemical-specific data):
    - Sugar beets at 3 & 4.95 lb. ai/A (MOEs = 7.4 and 4.5, respectively)

Closed Mixing/Loading and Closed-cab Application (i.e., engineering controls):

- Mixer/loader scenarios (using surrogate exposure data):
    - All scenarios (total MOE ranges from 0.12 to 0.99 ; LOC of 10)
- Applicator scenarios (using surrogate exposure data):
    - All scenarios (total MOEs ranges from <1 to 3.9; LOC of 10)

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Aldicarb Open Pour/Open Cab Application Using Label-Required PPE (Double layer of clothing and PF5 Respirator) Using Chemical-Specific Data									
Crop or Target	**Dermal Unit Exposure (µg/lb. ai)[1] [Level of PPE]**	**Inhalation Unit Exposure (µg/lb. ai)[1] [Level of PPE]**	**Maximum Application Rate (lb. ai/A)[2]**	**Area Treated Daily (Acres)[3]**	**Dermal**		**Inhalation**		**Total**
					Dose (mg/kg/day)[4]	**MOE (LOC = 10)[5]**	**Dose (mg/kg/day)[6]**	**MOE (LOC = 10)[7]**	**MOE (LOC = 10)[8]**
Mixer/Loader (Load Granules – tractor drawn spreader)									
Sweet potato [e.g., nematodes]	0.22 [DL/G]	0.014 [PF5]	3	80	0.00066	20	0.000042	310	19
			1.5		0.00033	39	0.000021	620	37
Sugar beets [e.g. nematodes]			4.95	200	0.00273	4.8	0.000174	75	**4.5**
Sugar beets [leafminers/leafhoppers]			3		0.00165	7.9	0.000105	120	**7.4**
Dry bean [nematodes]; Sugar beets [aphids]; Cotton [side-dress applications]			2.1		0.00116	11	0.0000735	180	10
Peanut [nematodes /post-pegging]			1.5		0.000825	16	0.0000525	250	15
Dry bean [aphids]; Cotton [nematodes]; Peanuts [nematodes/thrips]; Soybean [Mexican bean beetle/thrips]			1.05		0.000578	22	0.0000368	350	21
Dry bean [seedcorn maggot]; Cotton [aphids/thrips]; Soybean [nematodes/thrips]			0.75		0.000413	31	0.0000263	490	29
Applicator (granules – tractor-drawn spreader)									
Sweet potato [e.g., nematodes]	0.089 [DL/G]	0.0026 [PF5]	3	80	0.000268	49	0.0000078	1700	48
			1.5		0.000134	97	0.0000039	3300	94
Sugar beets [e.g. nematodes]			4.95	200	0.0011	12	0.0000321	400	12
Sugar beets [leafminers/leafhoppers]			3		0.000668	19	0.0000195	670	18
Dry bean [nematodes]; Sugar beets [aphids]; Cotton [side-dress applications]			2.1		0.000468	28	0.0000136	960	27
Peanut [nematodes /post-pegging]			1.5	200	0.000334	39	0.00000975	1300	38
Dry bean [aphids]; Cotton [nematodes]; Peanuts [nematodes/thrips]; Soybean			1.05		0.000234	56	0.00000683	1900	54

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Aldicarb Open Pour/Open Cab Application Using Label-Required PPE (Double layer of clothing and PF5 Respirator) Using Chemical-Specific Data									
Crop or Target	Dermal Unit Exposure (µg/lb. ai)[1] [Level of PPE]	Inhalation Unit Exposure (µg/lb. ai)[1] [Level of PPE]	Maximum Application Rate (lb. ai/A)[2]	Area Treated Daily (Acres)[3]	Dermal		Inhalation		Total
					Dose (mg/kg/day)[4]	MOE (LOC = 10)[5]	Dose (mg/kg/day)[6]	MOE (LOC = 10)[7]	MOE (LOC = 10)[8]
[Mexican bean beetle/thrips]									
Dry bean [seedcorn maggot]; Cotton [aphids/thrips]; Soybean [nematodes/thrips]			0.75		0.000168	77	0.00000488	2700	75

1 Based on MRID 43852501; The study inhalation unit exposure (0.07 µg/lb. ai) representative of baseline protection (i.e. no respirator) was adjusted to represent use of a PF5 respirator (i.e., 80% reduction in exposure). PF5 = a NIOSH-approved respirator with a dust-mist filter with MSHA/NIOSH approval number prefix TC-21 or any N, R, P or HE filter.
2 Based on registered label (Reg. No. 87895-00001).
3 Exposure Science Advisory Council Policy #9.1.
4 Dermal Dose = Dermal Unit Exposure (µg/lb. ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb. ai/acre) × Area Treated (A/day) × DAF (100%) ÷ BW (80 kg).
5 Dermal MOE = Dermal BMDL10 (0.013 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb. ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb. ai/acre) × Area Treated (A/day) ÷ BW (80 kg).
7 Inhalation MOE = Inhalation BMDL10 (0.013 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = BMDL10 (0.013 mg/kg/day) ÷ [Dermal Dose + Inhalation Dose].

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Aldicarb Engineering Controls									
Crop or Target	Dermal Unit Exposure (µg/lb. ai)[1] [Level of PPE]	Inhalation Unit Exposure (µg/lb. ai)[1] [Level of PPE]	Maximum Application Rate (lb. ai/A)[2]	Area Treated Daily (Acres)[3]	Dermal		Inhalation		Total
					Dose (mg/kg/day)[4]	MOE (LOC = 10)[5]	Dose (mg/kg/day)[6]	MOE (LOC = 10)[7]	MOE (LOC = 10)[8]
Loader (Load Granules – tractor drawn spreader)									
Sweet potato [e.g., nematodes]	8.6 [EC]	0.083 [EC]	3	80	0.0258	**0.5**	0.000249	52	**0.5**
			1.5		0.0129	**1**	0.000125	100	**0.99**
Sugar beets [e.g. nematodes]			4.95	200	0.106	**0.12**	0.00103	13	**0.12**
Sugar beets [leafminers/leafhoppers]			3	200	0.0645	**0.2**	0.000623	21	**0.2**
Dry bean [nematodes]; Sugar beets [aphids]; Cotton [side-dress applications]			2.1	200	0.0451	**0.29**	0.000436	30	**0.29**
Peanut [nematodes /post-pegging]			1.5	200	0.0323	**0.4**	0.000311	42	**0.4**
Dry bean [aphids]; Cotton [nematodes]; Peanuts [nematodes/thrips]; Soybean			1.05	200	0.0226	**0.58**	0.000218	60	**0.57**

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Aldicarb Engineering Controls									
Crop or Target	**Dermal Unit Exposure (µg/lb. ai)[1] [Level of PPE]**	**Inhalation Unit Exposure (µg/lb. ai)[1] [Level of PPE]**	**Maximum Application Rate (lb. ai/A)[2]**	**Area Treated Daily (Acres)[3]**	**Dermal**		**Inhalation**		**Total**
					Dose (mg/kg/day)[4]	**MOE (LOC = 10)[5]**	**Dose (mg/kg/day)[6]**	**MOE (LOC = 10)[7]**	**MOE (LOC = 10)[8]**
[Mexican bean beetle/thrips]									
Dry bean [seedcorn maggot]; Cotton [aphids/thrips]; Soybean [nematodes/thrips]			0.75	200	0.0161	**0.81**	0.000156	83	**0.8**
Applicator									
Sweet potato [e.g., nematodes]	2.0 [EC]	0.22 [EC]	3	80	0.006	**2.2**	0.00066	20	**2**
			1.5		0.003	**4.3**	0.00033	39	**3.9**
Sugar beets [e.g. nematodes]			4.95	200	0.0248	**0.52**	0.00273	4.8	**0.47**
Sugar beets [leafminers/leafhoppers]			3	200	0.015	**0.87**	0.00165	7.9	**0.78**
Dry bean [nematodes]; Sugar beets [aphids]; Cotton [side-dress applications]			2.1	200	0.0105	**1.2**	0.00116	11	**1.1**
Peanut [nematodes /post-pegging]			1.5	200	0.0075	**1.7**	0.000825	16	**1.5**
Dry bean [aphids]; Cotton [nematodes]; Peanuts [nematodes/thrips]; Soybean [Mexican bean beetle/thrips]			1.05	200	0.00525	**2.5**	0.000578	22	**2.2**
Dry bean [seedcorn maggot]; Cotton [aphids/thrips]; Soybean [nematodes/thrips]			0.75	200	0.00375	**3.5**	0.000413	31	**3.1**

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (September, 2015) as noted; Level of mitigation: Eng. Controls.
2 Based on registered label (Reg. No. 87895-00001).
3 Exposure Science Advisory Council Policy #9.1.
4 Dermal Dose = Dermal Unit Exposure (µg/lb. ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb. ai/acre) × Area Treated (A/day) × DAF (100%) ÷ BW (80 kg).
5 Dermal MOE = Dermal BMDL10 (0.013 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb. ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb. ai/acre) × Area Treated (A/day) ÷ BW (80 kg).
7 Inhalation MOE = Inhalation BMDL10 (0.013 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = BMDL10 (0.013 mg/kg/day) ÷ [Dermal Dose + Inhalation Dose].

11.2 Occupational Handler Risk Characterization

The occupational handler scenarios assessed represent low dust formulations, while the PHED data for the scenarios associated with Table 11.1.2 are from studies using clay granules which are known to be more friable (i.e., more dusty) than engineered low dust formulations such as used for aldicarb. The low-dust vinyl-coated scenarios associated with the closed loading scenario have lower exposure potential than the clay-based substrate surrogate in the PHED engineering control unit exposures.

HED notes that qualitatively the occupational exposure using engineering controls for any given handling or loading scenario is lower than the available chemical-specific handler data (occupational handlers with PPE) associated with Table 11.1.2. While the available chemical-specific study is representative of the low-dust formulation, it cannot be used to estimate exposure from the use of engineering controls (i.e., closed loading and closed cab applications). HED acknowledges that the unit exposures for the use of engineering controls with the low-dust formulation should be less than those identified in the study for use of open pour/open cab application. It is noted that based on the surrogate unit exposure guide, closed loading/closed cab systems often provide up to 90% reduction in exposure.

11.3 Short- and Intermediate-Term Post-Application Risk

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting.

11.3.1 Occupational Post-application Inhalation Exposure/Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for aldicarb.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the agency's risk assessments.

11.3.2 Occupational Post-application Dermal Exposure/Risk Estimates

A quantitative post-application dermal assessment has not been conducted for aldicarb because aldicarb is soil incorporated and there is limited potential for worker dermal exposure to soil incorporated pesticides.

In accordance with 40 CFR 158, dislodgeable foliar residue (DFR) data are required for all occupational (e.g., crop, nursery, greenhouse use sites) or residential (e.g., ornamental and vegetable gardens, pick your own farms, retail tree farms) uses that could result in post-application exposure to foliage. In the case of aldicarb, there are no currently labeled uses that would result in foliar residue; therefore, no DFR data are required at this time. In the case that the registered use pattern changes, HED would reevaluate the need for a DFR study, depending on the proposed label change.

The Restricted Entry Interval (REI) specified on the existing labels (48 hours) is based on the acute toxicity of aldicarb. Aldicarb is classified as Toxicity Category I *via* the dermal, oral, and inhalation routes of exposure. Due to severe effects (death) following corneal and dermal dosing, dermal and eye irritation studies were waived in the acute toxicity database. Because of the limited worker exposure profile (soil-incorporation), the REI on the labels is adequate to protect for worker exposure. Therefore, the (156 subpart K) Worker Protection Statement interim REI of 48 hours is adequate to protect agricultural workers from post-application exposures to aldicarb.

12.0 Human Incidents

One component of the Agency's registration review program is consideration of human observational information including incident data, medical case reports, general medical information, and epidemiology studies. In conjunction with a human health risk assessment based on other data sources, such human incident and other human data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products.

Based on the low frequency and severity of incident cases reported for aldicarb in both Incident Data System (IDS) and NIOSH SENSOR-Pesticides, there does not appear to be a concern at this time with respect to incident cases that would warrant further investigation. Additionally, the findings of the research reviewed from the Agricultural Health Study (AHS) do not support any changes to OPP's approach to quantitative risk assessment for aldicarb. However, OPP will continue to monitor the AHS and other epidemiologic results and will re-evaluate these conclusions as needed.

HED has prepared an aldicarb incident report review (E. Evans et al., 09/30/2014, D430435, Aldicarb: Tier I Update of Human Incidents for Draft Risk Assessment). The review considers a variety of types and sources of human observational information including human incident data, medical data/case report information, and epidemiological information in an effort to inform the re-evaluation of aldicarb in this phase of registration review. The human incident databases that were reviewed are:

- the OPP IDS;
- NIOSH's Sentinel Event Notification System for Occupational Risks (SENSOR);

OPP's IDS includes reports of alleged human health incidents from various sources, including mandatory FIFRA Section 6(a)(2) reports from registrants, other federal and state health and

environmental agencies, and individual consumers. Overall, there are few incidents involving aldicarb reported to IDS. Incidents in the IDS system include:

- For the Main IDS, from January 1, 2012 to April 28, 2015, there were 3 incidents reported for single chemical only in the database. There were no additional incidents reported involving more than one chemical. One incident was classified as major severity and the other two incidents were classified as moderate severity.
- In Aggregate IDS, from January 1, 2012 to April 28, 2015, there were 2 reported incidents involving aldicarb. These incidents were classified as minor severity.

A query of SENSOR-Pesticides from 1998-2011 identifies 79 single ai cases involving aldicarb (PC code 098301). Sixteen of these 79 cases have been removed from this analysis because they were intentional exposures. Therefore, 63 single ai case reports are relevant for the aldicarb registration review assessment.

In addition to the incident/poisoning data and medical case reports, epidemiological research can be an important source for human observational data and can potentially assist in identifying, characterizing, and (ideally) quantifying linkages between human exposures and resulting health effects. For aldicarb, epidemiological data is available from the AHS. Investigators with the AHS (Lee et al. (2007)) performed an analysis of colorectal cancer, looking at colon, rectal and colorectal (colon + rectal) cancer among AHS study participants. There were 40 aldicarb-exposed colorectal cancer cases and 195 non-exposed cases generating an OR of 1.6 (95% CI: 1.0, 2.4) when cases were classified by ever/never use. The authors also conducted an exposure-response assessment by dividing exposures into 4 levels (a non-exposed referent level and three tertile exposure levels) for colorectal, colon, and rectal cancers, but the numbers of cases in each category were small, ranging from a low of 1 to a high of 8. For the highest exposed groups ORs for colorectal cancer were 2.6 (95% CI: 0.9, 7.6; n= 5, p-trend 0.014) and for colon cancer 4.1 (95% CI 1.3, 12.8; n=5, p for trend 0.001). Overall, authors note the significance of the finding, but suggest caution due to small numbers, the role of chance, residual confounding factors, the lack of biological explanation and the fact that not all results were associated with an *a priori* hypothesis. Additionally, existing experimental evidence from the available animal toxicological database does not support the carcinogenicity determination for aldicarb.

In summary, the available incident report details available incident and epidemiological data. The available incident data identified 68 incidents, most being of minor or moderate severity and several being of major severity. About half involved agricultural incidents, although not all the incidents occurred for registered use patterns. The most commonly reported symptoms were gastrointestinal including diarrhea, vomiting and abdominal pain, followed by neurological symptoms including sweating and dizziness. Neurological symptoms are consistent with what would be expected for cholinesterase inhibition. Several of the cases experienced cardiovascular symptoms including chest pain and slow heartbeat. The available epidemiological data from the AHS do not support any changes to OPP's approach to quantitative risk assessment for aldicarb. OPP will continue to monitor incident data, the AHS and other epidemiologic results and will re-evaluate these conclusions as needed. (E. Evans et al., 09/30/2014, D430435).

13.0 References

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Lloyd, M. (2015). D430949. **Aldicarb:** Occupational and Residential Exposure Assessment in Support of Registration Review.

Swartz, C. (2000). D266396. **Aldicarb:** (List A Case 0140, Chemical ID No. 098301). Residue and Product Chemistry Chapters of the HED Reregistration Eligibility Decision Document (RED).

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for the food uses of aldicarb are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	no[A]
870.2500	Primary Dermal Irritation	yes	no[A]
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes[B]
870.3150	Oral Subchronic (non-rodent)	yes	yes
870.3200	21-Day Dermal	yes	no[C]
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	yes	no[C]
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (non-rodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (non-rodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation (bacterial)	yes	yes
870.5300	Mutagenicity—Gene Mutation (mammalian)	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5450	Mutagenicity—Dominant Lethal Test	yes	yes
870.5500	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	yes	yes
870.6100b	90-Day Neurotoxicity (hen)	CR	yes
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Develop. Neurotoxicity	yes	yes
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	-
870.7800	Immunotoxicity	yes	yes

[A] Eye and dermal irritation studies are not required due to lethality from these exposure routes.
[B]Chronic toxicity study satisfies this requirement.
[C]Not required due to severe irritation.
CR conditionally required.

A.2 Toxicity Profiles

Table A.2.1. Aldicarb Acute Toxicity Profile			
Guideline No./Study Type	**MRID No.**	**Results**	**Tox Category**
870.1100 Acute oral toxicity	00057333	LD_{50} = 0.8 mg/kg/day	I
870.1200 Acute dermal toxicity	00091241 00069916	LD_{50} = 20 mg/kg/day, water LD_{50} = 5 mg/kg, propylene glycol	I
870.1300 Acute inhalation toxicity	00069916 00057333	LC_{50} < 0.007 mg/L	I
870.2400 Acute eye irritation	00069916	No corneal irritation at lethal dose	N/A
870.2500 Acute dermal irritation	00069916	None at fatal levels	N/A
870.2600 Skin sensitization	N/A	N/A	N/A

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile of Aldicarb Technical		
Study Type [GLN No.]	**MRID No./Classification**	**Results[1]**
Sub-chronic oral toxicity (Beagle dog) [870.3150]	41919901 (1991) Acceptable/Non-guideline 0, 0.01, 0.02, or 0.06 mg/kg/day (diet) 14 weeks Cholinesterase samples 2-hours post dose	NOAEL=0.02 mg/kg/day LOAEL=0.06 mg/kg/day based on plasma and RBC AChEI in males and females
21-day dermal toxicity (CD® Sprague-Dawley rats) [870.3200]	44636101 (1998) Non-guideline/Unacceptable 0, 100, 250, or 500 mg/kg/day, 6 hours/day, 5 days/week for 3 weeks	Unacceptable due to inconsistent findings in body weight and cholinesterase inhibition; concerns for several aspects of the study (adequacy of skin contact with test material; wetting of test material; amount of skin exposed; limited data on active ingredient)

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile of Aldicarb Technical		
Study Type [GLN No.]	**MRID No./Classification**	**Results[1]**
Developmental toxicity rodent (Sprague-Dawley Crl:CD BR rats) [870.3700a]	41004501 (1988) Acceptable/Guideline 0, 0.125, 0.25, or 0.5 mg/kg/day GD 6-16 (gavage)	Maternal: NOAEL=0.125 mg/kg/day LOAEL=0.25 mg/kg/day Based on decreased body weight gain and food consumption. At 0.50 mg/kg/day (HDT), 3 dams died on Day 7. Significant increases in signs of AChEI (hypoactivity, ataxia, tremors, lacrimation, unkempt appearance, urine stains, loose stools, cold extremities, nasal and ocular crusting, audible respiration) were observed Developmental: NOAEL=0.125 mg/kg/day LOAEL=0.25 mg/kg/day based on ecchymosis of the trunk
Developmental toxicity in non-rodent (Dutch Belted rabbit) [870.3700b]	0132668 (1983) Acceptable/Guideline 0, 0.1, 0.25, or 0.5 mg/kg/day GD 7-27 (gavage)	Maternal: NOAEL=0.1 mg/kg/day LOAEL=0.25 mg/kg/day based on decreased body weight, pale kidneys and hydroceles on the oviducts Developmental: NOAEL=>0.5 mg/kg/day
Reproduction and fertility effects (Sprague-Dawley Crl:CD BR rats) [870.3800]	42148401 (1991) Acceptable/Guideline males: 0, 0.1, 0.4, 0.7, or 1.4 mg/kg/day females: 0, 0.2, 0.4, 0.9, or 1.7 mg/kg/day	Parental/Systemic: NOAEL=0.4 mg/kg/day LOAEL=0.7-0.9 mg/kg/day based on decreased body weight gains and RBC and plasma AChEI Reproductive: NOAEL=0.7-0.9 mg/kg/day LOAEL=1.4-1.7 mg/kg/day based on decreased viability and body weights, and signs of debilitation
Chronic oral toxicity in rodents (Sprague-Dawley Crl:CD BR rats) [870.4100a]	43045401 (1993) Acceptable/Guideline males: 0, 0.047, 0.47, or 1.44 mg/kg/day females: 0, 0.06, 0.59, or 1.87 mg/kg/day	NOAEL=0.047 mg/kg/day LOAEL=0.47 mg/kg/day based on plasma and RBC AChEI
Chronic oral toxicity dogs (Beagle) [870.4100b]	40695401, 42191501 (1988) Acceptable/Guideline 0, 1, 2, 5, 10 ppm (0, 0.028, 0.056, 0.13, or 0.25 mg/kg/day)	NOAEL<0.028 mg/kg/day LOAEL=0.028 mg/kg/day based on plasma AChEI

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile of Aldicarb Technical		
Study Type [GLN No.]	**MRID No./Classification**	**Results[1]**
Carcinogenicity in rats (Sprague-Dawley Crl:CD BR rats) [870.4200]	43045401 (1993) Acceptable/Guideline males: 0, 0.047, 0.47, or 1.44 mg/kg/day females: 0, 0.06, 0.59, or 1.87 mg/kg/day	NOAEL=0.047 mg/kg/day LOAEL=0.47 mg/kg/day based on plasma/RBC AChEI No evidence of carcinogenicity
Carcinogenicity in mice (CD-1) [870.4300]	00044732; 00044733; 00044734 (1972) Acceptable/Guideline 0, 0.1, 0.2, 0.4, or 0.7 mg/kg/day (diet)	NOAEL=0.2 mg/kg/day LOAEL=0.4 mg/kg/day based on increased mortality No evidence of carcinogenicity
Gene Mutation Chinese hamster ovary (CHO) cell HGPRT forward gene mutation assay [870.5300]	00148168 (1985) Acceptable/Guideline 1000-5000 µg/ml	Negative with and without activation at a marginally cytotoxic dose
Cytogenetics: Mammalian bone marrow chromosome aberration test ICR mouse [870.5385]	41661301; 41663102 (1990) Acceptable/Guideline 0.1-0.4 mg/kg	No chromosomal aberrations in mouse bone marrow cells
Unscheduled DNA Synthesis [870.5500]	00141673 (1984) Acceptable/Guideline 33-10,000 µg/well	No effects
Dominant Lethal Study (Sprague-Dawley rat)	43575101 (1995) Acceptable/Guideline	Systemic LOAEL=2.28 mg/kg based on body weight reductions, tremors, and plasma, RBC and brain AChEI No evidence of a dominant lethal effect
Acute neurotoxicity screening battery (Sprague-Dawley Crl:CD BR rats) [870.6200a]	43442301 (1994) Acceptable/Guideline 0, 0.05, 0.1, 0.5 mg/kg (gavage)	NOAEL<0.05 mg/kg/day LOAEL=0.05 mg/kg/day, based on plasma and RBC AChEI NOAEL = 0.05 mg/kg LOAEL = 0.1 mg/kg, based on brain AChEI

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile of Aldicarb Technical		
Study Type [GLN No.]	**MRID No./Classification**	**Results[1]**
Subchronic neurotoxicity screening battery (Sprague-Dawley Crl:CD BR rats) [870.6200b]	43829602 (1995) Acceptable/Guideline 0, 0.5, 0.20, 0.40 mg/kg/day (gavage) for 13 weeks	NOAEL<0.05 mg/kg/day LOAEL=0.05 mg/kg/day based on pinpoint pupils and blood and brain AChEI
Developmental neurotoxicity (Sprague-Dawley Crl:CD7 BR VAF/Plus 7 rats) [870.6300]	43829601 (1995) Acceptable/Guideline 0, 0.05, 0.10, or 0.30 mg/kg/day GD 6-LD 10 (gavage)	Maternal: NOAEL=0.05 mg/kg/day LOAEL=0.1 mg/kg/day based on plasma AChEI RBC AChEI at 0.1 mg/kg/day 16% (LD 7); 11% (LD 11) not statistically significant; at 0.3 mg/kg/day, GD 7/LD 7 AChEI 27% Offspring: NOAEL=0.05 mg/kg/day LOAEL=0.1 mg/kg/day based on reduced body weights and decreased motor activity
Metabolism and pharmacokinetics [870.7485]	00102022 (1966) 00102023 (1967) Acceptable/Guideline	85% of an acute oral dose to rats was excreted in 24 hours. The metabolism of aldicarb was primarily to the sulfoxide (40%), with a smaller amount then slowly converted to the sulfone
Immunotoxicity Study (Swiss Webster or B6C3F1 mice) [870.7800]	00410546 (1989) Acceptable/Guideline (published paper)	Aldicarb had no significant effect on numbers and percentages of splenic total T-lymphocytes, T-helper cells, T-suppressor/cytotoxic cells, or B-cells when administered to female B6C3F1 mice at 1, 10, or 100 ppb in drinking water for 34 days. Additionally, there was no significant effect on either splenic natural killer cell function or cytotoxic T-cell function

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile of Aldicarb Technical

Study Type [GLN No.]	MRID No./Classification	Results[1]
Comparative cholinesterase (Sprague-Dawley Crl:CD BR rats)	47994302-47994303 (2009) 47994304-47994305 (2010) Acceptable/Non-guideline Adults: 0, 0.03, 0.05, 0.065, 0.08, 0.15, or 0.3 mg/kg PND 11 pups: 0, 0.005, 0.01, 0.02, 0.04, or 0.08 mg/kg	PND 11 pups showed sensitivity for both RBC and brain cholinesterase inhibition **Results of BMD Modeling (mg/kg) for Brain and RBC Cholinesterase, Acute Oral Dosing Studies in Rats (CCA)** **Study** / **Age/Sex** / **Brain BMD_{10}** / **Brain $BMDL_{10}$** / **RBC BMD_{10}** / **RBC $BMDL_{10}$** MRID 47994302-05 Acute CCA[A] / PND 11 Male / 0.0143 mg/kg / 0.0112 mg/kg / 0.00477 mg/kg / 0.00387 mg/kg MRID 47994302-05 Acute CCA[A] / PND 11 Female / 0.0136 mg/kg / 0.0103 mg/kg / 0.00731 mg/kg / 0.00387 mg/kg MRID 47994302-05 Acute CCA[A] / Adult Male / 0.0535 mg/kg / 0.0484 mg/kg / 0.0228 mg/kg / 0.0153 mg/kg MRID 47994302-05 Acute CCA[A] / Adult Female / 0.0615 mg/kg / 0.0498 mg/kg / 0.0242 mg/kg / 0.0144 mg/kg
Special neurotoxicity studies: Moser VC (Long-Evans rats)	45068601 (1999) TAP 157 94-106	NOAEL<0.05 mg/kg LOAEL=0.05 mg/kg (pups) Effects in pups: Blood (both sexes), brain AChEI (males). Note: PND 17 day pups exhibited twice the level of brain AChEI as adults
Acute oral study (human)	42373001 (1992) 46131001 (supplementary report) Acceptable/Non-guideline Males: 0, 0.01, 0.025, 0.06, 0.06, or 0.075 mg/kg Females: 0, 0.025, or 0.05 mg/kg	NOAEL = not determined for females LOAEL = 0.025 mg/kg, based on RBC cholinesterase inhibition NOAEL = 0.01 mg/kg LOAEL = 0.025 mg/kg, based on clinical signs and RBC cholinesterase inhibition in males

[1]NOAEL = No observed adverse effects level; LOAEL = Lowest observed adverse effects level; AChE = Cholinesterase; AChEI = Cholinesterase inhibition; RBC = red blood cell.

Table A.2.1 Summary of Benchmark Dose (BMD) Analyses for RBC and Brain AChEI from Acute CCA Studies

Table 2.3. Results of BMD Modeling (mg/kg) for Brain and RBC Cholinesterase, Acute Oral Dosing Studies in Rats					
Study	**Age/Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 47994302-05 Acute CCA[A]	PND 11 Male	0.0143 mg/kg	0.0112 mg/kg	0.00477 mg/kg	0.00387 mg/kg
MRID 47994302-05 Acute CCA[A]	PND 11 Female	0.0136 mg/kg	0.0103 mg/kg	0.00731 mg/kg	0.00387 mg/kg
MRID 47994302-05 Acute CCA[A]	Adult Male	0.0535 mg/kg	0.0484 mg/kg	0.0228 mg/kg	0.0153 mg/kg
MRID 47994302-05 Acute CCA[A]	Adult Female	0.0615 mg/kg	0.0498 mg/kg	0.0242 mg/kg	0.0144 mg/kg

MRID 47994302-47994305; samples taken at peak effect times: 40 minutes (adults)/60 minutes (PND 11 pups).

A.3 Executive Summaries

A.3.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity - Rat

870.3100 90-Day Oral Toxicity - Mouse

870.3150 90-Day Oral Toxicity - Dog

EXECUTIVE SUMMARY: In this subchronic dietary study (MRID 41919901), 6 Beagle dogs/sex/dose were exposed for 14 weeks to 0, 0.01, 0.020, or 0.06 mg/kg/day of aldicarb [99.7%] *via* the diet (at levels of 0, 0.35, 0.7 or 2 ppm). Plasma and RBC cholinesterase levels were determined at -3, -2, and -1 weeks prior to dosing and at 2 and 5 weeks after dosing began. Blood was taken ~2 hours after a limited 2 hour feeding period. Weekly body weights and daily food consumption were assessed. Hematology and urinalysis were performed on samples taken at 1 week prior to dosing and at 5 weeks. Ophthalmoscopic exams were performed on all dogs prior to treatment and during week 5, using an indirect ophthalmoscope. After 14 weeks on study, all dogs were sacrificed and gross pathological exams were performed.

There were no effects on body weight, food consumption, urinalysis measures, ophthalmoscopic exams or gross pathology exams. Statistically significant effects were seen in hematological measures in high dose males (longer mean clotting time of 0.06 mg/kg), or high dose females (shorter prothrombin time of 0.02, 0.06 mg/kg), and in clinical chemistry in reduced serum calcium in females (0.01 mg/kg and 0.02 mg/kg), but their toxicological significance was unclear.

In females, at 0.06 mg/kg, there were decreases in plasma cholinesterase where 5 of 6 dogs showed greater than 20% inhibition (range 19-32%) after 2 and 5 weeks. Effects on RBCs were smaller (range +5 to -17%). At lower doses, effects were smaller in plasma (range 0-16%) and RBCs (range +12-23%). In males, at 0.06 mg/kg, there were decreases in plasma cholinesterase after 2 weeks (range 24-40%) and after 5 weeks (range 17-42 %). Decreases in RBC cholinesterase were seen after 2 weeks (range 4.5-22%) and at 5 weeks (range 12-27%). At 0.02 mg/kg, one dog showed inhibition in plasma of 25.9% after 2 weeks (range 7-26%), as well as after 5 weeks, 22% (range 13-22%). RBC cholinesterase deficits were also smaller at this dose level after 2 weeks (range + 1%-13%) and 5 weeks (range 1%-18%). Brain cholinesterase was not measured.

Stimulation of gut motility was noted as an increase in occurrence of mucoid or soft stool for some male dogs at all dose levels in comparison to any male control dog. This data was not analyzed statistically, nor compared with the incidence in each dog prior to exposure. The reviewer concluded this to be "suggestive of a local tissue effect and not indicative of a serious toxic effect".

NOAEL = 0.02 mg/kg. LOAEL = 0.06 mg/kg based on plasma and RBC cholinesterase inhibition in male and female dogs.

The subchronic oral toxicity study in the dog is classified **Acceptable/Non-Guideline**, and alone does not satisfy the guideline requirement [OPPTS 870.3150] for a subchronic oral toxicity study in the non-rodent. Its purpose was to establish an NOAEL for AChEI, which was achieved. In combination with the one year dog study (MRID 40695901), these studies provide sufficient data to satisfy both the non-rodent subchronic and chronic toxicity study data requirements [82.1(b)/83-1; OPPTS 870.3150/870.4100].

870.3200 21/28-Day Dermal Toxicity – Rat

EXECUTIVE SUMMARY: In this 21 day dermal toxicity study (MRID 44636101), Temik 15G® grit [14.75% aldicarb] was dermally applied to a 1" square area on the backs of 8 albino CD® Sprague-Dawley rats/sex/dose at levels of 0, 100, 250, or 500 mg/kg/day, for 6 hours/day, 5 days/week, for 3 weeks. In preliminary studies, Temik was applied once at 1000 mg/kg to 3 rats/sex for 6 hours (I), and to 5 male rats at 0, 250, 500, or 1000 mg/kg/day for 6 hours/day for 3 days (II). In II, a positive control group of 5 male rats were given an oral gavage dose of 0.1 mg/kg of aldicarb technical [99.5% ai].

There were no deaths or treatment related clinical signs noted in the study. In males, there were significant reductions in overall body weight gain (based on effects on days 15-19) at 100 mg/kg (21%) and 250 mg/kg (27%) but the decrease at 500 mg/kg group (11%) was not significant. There were correlative significant decreases in food consumption for days 15-19 in the 250 mg/kg males (12.7 %, g/day) but not at 100 mg/kg. In II, plasma and RBC AChE were significantly decreased at 500 mg/kg (plasma 46-50%; RBCs 14-26%) and 1000 mg/kg (plasma 35-72%; RBC 31-40%). In the definitive study, statistically significant AChEI was seen only in the plasma of males at the mid-dose 250 mg/kg (18-25%). There were no significant effects on brain AChEI in II (9.9% at 1000 mg/kg) or the 21 day study (3.4% at 500 mg/kg).

The LOAEL is 100 mg/kg based on reduced body weight gain. The NOAEL < 100 mg/kg.

The study should be regarded as **Unacceptable/Not upgradable,** based on the inconsistent findings in body weights and AChEI in the definitive study.

EXECUTIVE SUMMARY: In this 5 day dermal toxicity study (MRID 45079704), 5 mg/kg of analytical grade aldicarb in deionized water, or Temik 15G® grit [14.75% aldicarb] at levels of 0, 100, 500, or 2000 mg/kg/day was dermally applied to a 1" square area on the backs of 8 albino CD® Sprague-Dawley rats/sex/dose, for 6 hours/day, for 5 days. Body weights and clinical observations were recorded daily, and food consumption measured on Day 1 and Day 5. Blood cholinesterase measures were made on 0.25 ml samples taken 1 hour post-dosing on Day 1 and Day 5. On Day 5 after blood sampling, brain weights and brain AChE measures were made.

There was one female death in the 5 mg/kg technical aldicarb positive control group. In that 5 mg/kg group, cholinergic signs, including tremors, salivation, lacrimation, lethargy, and prostration, were seen in 1 or 2 females on days 3-5. Tremors were seen in 1 male and 2 females in the 2000 mg/kg Temik group one hour after dosing on days 1-3. Males in the 5 mg/kg aldicarb group showed decreased body weight gain (85%) and body weight decreases (7%) on days 4-5. There were no effects on food consumption, brain weights, or on necropsy (except for the dead female, who showed lacrimation, salivation, dark tar-like ano-genital discharge, darkened uterus, and autolysis of brain and digestive tract).

The 5 mg/kg rats showed 52-64% plasma AChEI, 29% RBC AChEI, on day 1, 62-90% plasma AChEI, 27-45% RBC AChEI, and 12-26% brain AChEI on day 5. Females showed greater effects on the brain than males, and greater effects on blood AChEs after five days of exposure.

Rats exposed to Temik at 2,000 mg/kg showed 90-94% plasma AChEI, 46-49% RBC AChEI, and 31% (males) and 51% (females) brain AChEI. Little change across the 5 days was seen at this dose, though females showed more brain inhibition than males. At 500 mg/kg Temik exposure caused significant inhibition in RBCs in both males (18-22%) and females (13-19%); and significant inhibition in plasma in males (33-50%), but not females (13-27%). Brain AChEI was slight (4-6%). Inhibition was greater on day 5 in plasma for both sexes. Rats exposed to Temik at 100 mg/kg showed no significant effects on brain or blood AChEI, though the effect on RBCs in females (12%) approached the statistically significant level seen in females (13%) in RBCs at 500 mg/kg.

This non-guideline study should be regarded as **Unacceptable**. It provides positive control data on dermal exposure to one dose of aldicarb technical, and comparable data on Temik 15G exposure, although the continuing concerns about the adequacy of the exposure preparation limit its utility for risk assessment. While it provides some interesting data on dermal exposures to both Temik and technical grade aldicarb, because of the unique aspects of the preparation, e.g., limited exposure area, limited wetting, and limited skin contact, it is difficult to compare these results to guideline dermal studies. Because the positive control data were collected on technical grade aldicarb dissolved in water makes comparison to granules (where only skin was slightly moistened) flawed and likely to make differences between technical aldicarb and Temik granules appear greater than they are. Because the positive control data also used a smaller surface area than is called for in guideline studies, they provide a distorted estimate of the relation between these dermal exposures and the oral exposure database in relation to how other materials are compared. The deficiencies in both of the rat studies, and the limited study duration, do not provide sufficient data to remedy the deficiencies in the earlier 21 day rat study and the database related to the dermal toxicity of aldicarb.

870.3465 90-Day Inhalation – Rat

There is no repeat dose inhalation toxicity study available. Additionally, there are no cholinesterase activity data available for aldicarb following inhalation exposure. However, HASPOC has recommended a study wavier for inhalation toxicity (TXR# 0057355, dated March 1, 2016).

A.3.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study - Rat

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 41004501), 25 mated female CD® (Sprague-Dawley) rats/group were given 0, 0.125, 0.25, or 0.5 mg/kg/day of aldicarb [99.5%] by gavage from days 6-15 of gestation. Dosing volume was kept constant at 1 ml/kg.

Three dams in the high dose group died on day 7. Other dams given this dose showed significant increases in signs of AChEI, including: hypoactivity, ataxia, unkempt appearance, urine stains, tremors, lacrimation, loose feces, cold extremities, nasal and ocular crusting, and audible respiration. Dams at the two highest dose levels (0.25 mg/kg and 0.5 mg/kg/day) showed significantly reduced body weight gain (13% and 26%, respectively) in comparison to controls. Food consumption was also significantly depressed for these groups (11% and 32%, respectively). There were no treatment related findings on gross pathology of the dams or on reproductive indices, e.g., implantations, corpora lutea, viable or dead fetuses, resorptions, or sex ratio. There was a significant decrease in the mean fetal weight (11%) in the offspring of high dose dams. There was a significant increase in ecchymosis of the trunk (as well as combined with ecchymosis of the extremities) in the 0.25 and 0.5 mg/kg offspring. At 0.5 mg/kg, an increased incidence (36% vs. 4% controls) of dilated lateral ventricles with tissue depression and a significant increase in poor ossification of the sixth sternebra (54% vs. 9% controls) were also found. No other effects were seen.

The maternal toxicity LOAEL = 0.25 mg/kg/day based on decreased body weight gain and food consumption. The maternal toxicity NOAEL = 0.125 mg/kg/day.

The Developmental LOAEL = 0.25 mg/kg/day based on ecchymosis of the trunk (small blood stained areas under the skin). The Developmental NOAEL = 0.125 mg/kg/day.

The developmental toxicity study in the rat is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.3700; §83-3*(a)*] for a developmental toxicity study in the rodent.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00132668), 16 pregnant Dutch Belted rabbits/group were given 0, 0.1, 0.25, or 0.5 mg/kg/day of aldicarb [99%] by gavage from days 7-27 of gestation. Dosing volume was kept constant at 1 ml/kg. Females were artificially inseminated, and this was considered day 0 of gestation.

After a mis-dosing on Day 7 (1st day of dosing) in which 8 rabbits/dose received 3 ml/kg instead of 1 ml/kg, and 5/8 rabbits in the 0.5 mg/kg group died, all mis-dosed rabbits were replaced. Survival thereafter was comparable for all maternal groups. In the dams at 0.25 and 0.5 mg/kg, there were compound related decreases in body weight (4-5.3%) during dosing, and pale kidneys and hydroceles on the oviducts were noted.

There were no compound related effects on skeletal or visceral malformations, or developmental variations. The number of implantations/dam (9.8, 6.1*, 7.2, 7.8) and viable fetuses/dam (8.7, 5.0*, 6.5, 6.2) were reduced at all dose levels, but they were only statistically significant (*) at the lowest dose. These were concluded not to be compound related because of the unusually large number of corpora lutea/dam (13.8, 11.3, 13.4, 12.8) and the low rate of pre-implantation loss in the control group (31%, 43%, 46%, 35%), both of which contributed to the higher number of viable fetuses and implantations in the control group. The available historical control data also supported this conclusion, with 4.4-7.8 implantations/dam, and 4.1-7.6 viable fetuses/dam.

The maternal toxicity LOAEL = 0.25 mg/kg/day based on decreased body weight, pale kidneys, and hydroceles on the oviducts. The maternal toxicity NOAEL = 0.1 mg/kg/day.

Developmental NOAEL > 0.5 mg/kg/day, the highest dose tested.

This developmental toxicity study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.3700; §83-3*(b)*] for a developmental toxicity study (non-rodent).

A.3.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

EXECUTIVE SUMMARY: In a 2-generation reproduction study (MRID 42148401), groups of 26 Crl:CD BR rats/sex/dose were administered doses of 0, 2, 5, 10, and 20 ppm (males: 0, 0.1, 0.4, 0.7, and 1.4 mg/kg/day and females: 0, 0.2, 0.4, 0.9, and 1.7 mg/kg/day) of aldicarb [99.7%] in the diet for 70 days prior to mating. Dosing continued as they were then mated twice and each generation of offspring (F_{1a} and F_{1b}) were raised and bred.

No treatment related deaths or clinical signs were noted in F_0 parents. Aldicarb consistently affected body weight in both the parents and offspring at the high dose, and in F_0 females at 0.9 mg/kg. At 0.9 mg/kg, decreased body weight gains (>96%) in the F_0 females during the first week of lactation of the first breeding were noted.

Aldicarb treatment also caused lower survivability and pup weights in offspring in the high dose F_{1a}, F_{2a}, and F_{2b} breedings. There was reduced viability in F_{1a} pups (viability index 78% vs. 96% in controls) and F_{2b} pups (56% viability vs. 89% controls) on day 4. For F_{2a} pups, there were fewer live pups/litter (28%). High dose F_{2b} pups also showed signs of debilitation: weak, thin, dehydration. High dose pup weights were significantly lower on days 14-21 in: F_{1a} females (10%); in F_{1b} males and females (13-20%); and F_{2a} males and females (7-14%).

Significant AChEI was observed at the highest dose level in F_0 males (29%,plasma; 23% RBC) and F_0 females (30%, plasma; 21% RBC) and in F_1 males (36%, plasma; 17%-26% RBC) and F_1 females (29%, plasma; 21%-22% RBC) both prior to mating and at termination. At the next highest dose level (0.7(M)-0.9(F) mg/kg group), RBC AChEI was observed in F_0 females (11%) at termination and plasma AChEI was observed in F_1 males (18%) prior to breeding.

The parental LOAEL was 0.7- 0.9 mg/kg based on decreased body weight gains in the F_0 females; RBC AChEI (F), and plasma AChEI (M). The parental NOAEL was 0.4 mg/kg for both sexes.

The reproductive LOAEL was 1.4 - 1.7 mg/kg based on decreased pup body weights (10%) in F_{1a}, F_{1b} and F_{2a} pups; reduced viability in F_{1a} and F_{2b} pups on day 4; and signs of debilitation in F_{2b} pups.

The reproductive NOAEL was 0.7-0.9 mg/kg.

This 2-generation reproduction study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.3800; §83-4] for a multi-generation reproduction study in the rat.

A.3.4 Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

EXECUTIVE SUMMARY: In a two year combined chronic toxicity/carcinogenicity study (MRID 43045401), aldicarb technical [99.7% ai] was administered in the diet to groups of 80 male and 80 female Sprague-Dawley Crl:CD BR rats for either 52 weeks or 104 weeks at dose levels of 0, 1, 10, and 30 ppm (0.047 mg/kg, 0.47 mg/kg, and 1.44 mg/kg for males and 0.06 mg/kg, 0.59 mg/kg, and 1.87 mg/kg for females).

There was no treatment-related effect on survival in either sex. Clinical signs were observed mainly at the high-dose level and included limited use of the tail, which was characterized as limpness and reduced tail movement. This sign became apparent in both sexes after 9-10 months of dosing, but the degree of limited tail use did not appear to worsen with time of exposure, and the hindlimbs remained fully functional. Alopecia was another prominent sign observed most frequently at the high-dose level in both sexes, and there was an increased incidence of soft feces in the high-dose males compared to the control males.

At the high-dose level (30 ppm), male and female rats showed decreased mean body weight (7-15% for males, 5-10% for females) and body weight gain (23%, males; 9%, females; for weeks 1-104; 16%, males; 19%, females for weeks 1-13). Ophthalmoscopic abnormalities were also evident at 30 ppm in the form of ectopic pupil and damage to the iris.

Significant inhibition of both red blood cell (18-40%, males; 30-42%, females) and plasma cholinesterases (46-58%, males; 31-53% females) were seen in both sexes given 30 ppm at all time-points, i.e., weeks 26, 52, 78, and 105. At 10 ppm, in male rats, significant decreases were also seen in plasma AChE at week 52 (27%) and RBC AChEs at weeks 26, 52, and 78 (12-15%). There was no significant effect in plasma or red blood cells at 1 ppm.

There was significant inhibition in brain AChE in females at 30 ppm (8-12 %), while males showed smaller changes (5%). There were no significant effects in brain at 10 ppm or 1 ppm.

There was some evidence of a neurotoxic effect at 30 ppm in both sexes, including tail paralysis, sciatic and tibial nerve degeneration and coccygeal and tail muscle atrophy and degeneration but, with the exception of tail paralysis, the differences were not statistically significant from control rats.

There was no evidence of carcinogenicity for aldicarb technical in this study. Dosing was considered adequate in both sexes based on treatment related inhibition of plasma, RBC, and brain AChEI and decreased body weight gain at 30 ppm.

The LOAEL is 10 ppm (0.47 mg/kg) based on significant plasma and RBC AChEI in male rats.

The NOAEL is 1 ppm (0.047 mg/kg).

The study is classified as **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.4300] for a combined chronic toxicity/carcinogenicity study in rats.

870.4100b Chronic Toxicity - Dog

EXECUTIVE SUMMARY: In a 1 year dog feeding study (MRID 40695901), groups of 5 beagle dogs/sex/dose were administered aldicarb technical in the diet daily for 52 weeks at 0, 1, 2, 5, and 10 ppm (0, 0.028, 0.056, 0.13, and 0.25 mg/kg/day). Blood (plasma and RBC) cholinesterase determinations were made 3 times prior to exposure and during weeks 5, 13, 26, and 52, two hours after the 2 hour feeding period. Brain measures were made at study termination. No effects were seen on mortality, body weight gain, food consumption, clinical chemistry, hematology, urinalysis, organ weights, ophthalmology, gross pathology or histopathology. At 0.05 mg/kg and above, dogs showed an increased incidence of signs of cholinesterase inhibition, including diarrhea and mucoid and/or soft stool. At 0.05 mg/kg and above, there was significant inhibition seen in plasma AChE (17-36%). There were decreases in RBC cholinesterases (14-28%), but they were not statistically significant until 0.13 mg/kg in males, or 0.25 mg/kg in females. Non-significant decreases ranged from 21-34% in males, and 14-28% in females at these doses. At 0.028 mg/kg/day, there was significant plasma cholinesterase inhibition in males (18-26%). Brain cholinesterase was significantly inhibited only at 0.25 mg/kg in males (22%). Based on plasma AChEI, a NOAEL for AChEI in the study was not established **(LOAEL = 0.028 mg/kg, based on plasma AChEI in males)**. To establish an NOAEL for blood AChEI, the registrant conducted a special 5 week feeding study in dogs (see under 870.3150, above).

The chronic oral toxicity study in the dog is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.3150] for a chronic oral toxicity study in the non- rodent. In combination with the subchronic oral toxicity dog study (MRID 40695901), whose purpose was to establish an NOAEL for AChEI (which it achieved), these studies provide sufficient data to satisfy both the non-rodent subchronic and chronic toxicity study data requirements [OPPTS 870.3150/870.4100].

A.3.5 Carcinogenicity

870.4200a Carcinogenicity Study - rat

See under 870.4100a (Chronic Toxicity above).

870.4200b Carcinogenicity (feeding) - Mouse

EXECUTIVE SUMMARY: In a mouse carcinogenicity study (MRID 00044732-00044734), aldicarb [99%] was administered in the diet to groups of 44 male and 44 female Charles River CD-1 mice at levels of 0, 0.1, 0.2, 0.4, or 0.7 mg/kg/day for 18 months.

During the first 3 months, there were statistically significantly (*) increased incidences of mortality seen in the males at 0.4 and 0.7 mg/kg (0/44, 1/44, 4/44, 7/45*, 9/44*) and females at 0.2, 0.4, and 0.7 mg/kg (0/44, 1/44, 8/44* 9/47* 8/44*). This was attributed to undissolved crystals of aldicarb, and thus inconsistent and excessive dosing. In response, aldicarb was thereafter dissolved in acetone prior to mixing in the diet. After 90 days, no treatment related differences in mortality were seen at any time-point. Cumulative mortality for the whole study among males given 0.4 and 0.7 mg/kg

was significantly increased at 41% for both dose groups (survival for both sexes was 59% or greater). There were no effects on body weight or body weight gain. In males that survived to terminal sacrifice, there were significant increases in hepatomas in the 0.1 and 0.7 mg/kg, but not 0.2 or 0.4 mg/kg groups: (1/37, 3%; 7/33*, 21%; 2/26, 8%; 6/30, 20%; 7/25*, 28% in increasing dose order).

When the animals sacrificed were included, only the increase at 0.7 mg/kg was statistically significant (8/33* vs. 2/39 controls). In males in the 0.7 mg/kg group, there were also significant increases in lymphoid neoplasias (0/39, 0/34, 4/30, 2/32, 7/33*) (<3%, <3%, 13%, 6%, 21%*). These were all due to mice that died on study (0/2, 0/1, 4/4, 2/2, 7/8). No other effects were seen.

This study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.4200] for a carcinogenicity study in mice.

EXECUTIVE SUMMARY: In a follow up 18 month mouse carcinogenicity study, groups of 50 male CD-1 mice were fed diets containing 0, 0.1, 0.3, or 0.7 mg/kg/day of aldicarb [99%; dissolved in acetone] (MRID 00044733). Three concurrent control groups were used: for one group (C), one mouse was killed each day one exposed mouse died; the other two groups were untreated (A, B).

There were no differences in overall mortality between the dosed and control groups (A, 30%; B, 12%; 0.1, 26%; 0.3, 24%; 0.7, 30%). There were no significant effects on body weight. There were no treatment related increases in any tumors in comparison to the control groups, except for lymphoid neoplasias in 0.1 and 0.7 mg/kg animals that died, but only when compared to group C, the day of death matched controls. (A, 5/11, 45%; B, 1/5, 20%; C, 0/18, <5.6%; 0.1, 6/10, 60%; 0.3, 2/5, 40%; 0.7, 3/7, 43%). In that group (C), no neoplasias were seen, while in the other controls, the incidences were greater and not significantly different from the treated groups. The study authors rejected this group as non-random. These findings were also not dose dependent. It was concluded that the study was negative.

This study is classified **Acceptable/Non-guideline**; it is non-guideline due to the use of one sex. The study was designed to replicate the findings of the first study and is considered acceptable for that purpose.

A.3.6 Mutagenicity

Gene Mutation

Guideline 870.5100 Reverse Mutation MRID 00042482 Classification: **Acceptable/Guideline**	Analytical Standard Temik (aldicarb) was tested with and without metabolic activator in stains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 of *Salmonella typminurium* at 5000, 1666, 500, 166 and 50 µg/plate. All results were negative. All positive and solvent controls were found within the acceptable range of historical mean data. Aldicarb: 50, 166, 500, 1666, 5000 µg/plate (+ or -) metabolic activation. Negative in strains TA1535, TA1537, TA1538, TA98 and TA100. Aldicarb Sulfoxide: 50, 166, 500, 1666, 5000 µg/plate (+ or -) metabolic activation. Negative. Aldicarb Sulfone: 100, 333, 1000, 3333, and 10000 µg/plate, [concentrations from MRID 46765102] (+ or -) metabolic activation. Negative.

Guideline 870.5300 CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay MRID 00148168 Classification: **Acceptable/Guideline**	In a mutagenicity study (MRID 00148168), aldicarb technical was evaluated in the CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay at doses of 1000, 2000, 3000, 4000, and 5000 µg/mL with and without metabolic (S9) activation. There were no significant or dose-related increases in mutant frequency at the HGPRT locus vs. negative and solvent controls in CHO cells in this study. The positive controls used in this study elicited the appropriate responses. Aldicarb: Under the conditions of the Chinese hamster ovary (CHO) cell HGPRT forward gene mutation assay, doses of aldicarb ranging from 1000 to 5000 µg/mL did not induce a mutagenic response either in the absence or the presence of rat liver microsomes. The maximum dose tested (5000 µg/mL) was marginally cytotoxic. Based on these findings, it was concluded that aldicarb was tested in a well-conducted study over an appropriate range of concentrations, with no evidence of a mutagenic effect.

Cytogenetics

Guideline 870.5450 Dominant Lethal MRID 43575101 Classification: **Acceptable/Guideline**	In a dominant lethal assay (MRID 43575101), groups of 40 male CD® (Sprague-Dawley) rats were fed dietary concentrations of 0, 7.5, 15 or 30 ppm aldicarb technical [98.9%] for 10 weeks. Actual intake, based on feed consumption and body weight was approximately 0.57, 1.11 and 2.28 mg/kg/day. Males were mated at a 1:1 ratio with untreated females once weekly for 2 weeks. Satellite groups of 10 male/group, receiving 0 or 30 ppm aldicarb technical test diets, were sacrificed after 4 days of dosing; recovered plasma, RBC and brain samples were assayed for AChE activity. The systemic toxicity LOEL is 30 ppm (2.28 mg/kg/day). Compound toxicity at 30 ppm was manifested as significant body weight reductions; significantly reduced body weight gain and feed consumption; fine motor tremors (approximately 13% of the animals); and significant inhibition of plasma (89%), RBC (35%) and brain (30%) AChE activity. The NOEL for AChEI was not established since AChE activity was not evaluated in the lower treatment groups. There was, however, no evidence that aldicarb technical induced a dominant lethal effect in male germinal cells treated over the entire period of spermatogenesis.

	dose range and brief conclusions of study (see gene mutation summary instructions) **MRID 146613012**. Under the conditions of this assay, the single oral gavage administration of 0.1, 0.2, or 0.4 mg/kg aldicarb did not cause a significant increase in the frequency of structural chromosome aberrations in bone marrow cells harvested from groups of 5 male and 5 female mice 6, 18, and 30 hours post exposure. Dose selection for the cytogenicity assays was based on the findings of a preliminary acute dose range-finding study which indicated that the combined oral LD_{50} for male and female mice was 0.48 mg/kg (0.33 to 1.04 mg/kg). In agreement with the preliminary results, mortality and other signs of compound toxicity (dyspnea and tremors) were seen in both sexes receiving 0.4 mg/kg of the test material. We conclude, therefore, that an appropriate range of concentrations was tested and that aldicarb was negative in a well-controlled assay. The study satisfies **Acceptable/Guideline** requirements for genetic effects Category II, Structural Chromosome Aberrations. **MRID 00142079**. The findings stated the total chromosomal aberration as well as the average number of aberrations per cell for all treated group was not significantly ($p > 0.05$) increased relative to the negative control group by the statistical analysis. Under the test conditions reported, the test compound was not considered to be clastogenic in the mouse bone marrow cytogenetic assay. However, the following inadequacy in reporting of this study must be clarified: The maximum tolerated dose selected for this study was not considered to be adequate. At least three dose levels should be used. The highest dose tested should produce some indication of toxicity as evidence by animal morbidity or target cell toxicity. Classified as **Unacceptable**. **MRID 00142081**. Under the test conditions reported, the test compound aldicarb Technical, did not induce any significant changes in the nuclear labeling of primary rat hepatocytes and exhibited no dose-related response at the dose ranges tested (33.3 through 3333.3 µg/well). Therefore, the test compound was considered to be inactive in the primary rat hepatocyte UDS assay. However, the following deficiencies in reporting of this study must be clarified: No statements of justification were made to the section of the nuclear and background counts of 20 cells for each treatment study. Ideally, 50 randomly selected cells of each of three slides per dose level should be used. Classified as **Unacceptable**. **TXR 0004462**. The provided explanation for the total nuclei (60) in each treatment condition and the evaluation criteria based on an increase of the mean nuclear grain count to at least 5 grains per nucleus in excess of the concurrent negative control value are considered to be reasonable and acceptable. Under the test conditions reported, the test compound, aldicarb, failed to induce any significant changes in the nuclear labelling of primary rat hepatocytes at any level of concentrations tested (33.3 to 10000 µg/well). In contrast, the positive control (2-AAF) apparently induced an expected high net grain count per nucleus in the range of 15.7 + or – 2.9. Therefore, the test results have provided conclusive evidence for the lack of UDS by the test compound in this assay system. The study is **Acceptable**.

EXECUTIVE SUMMARY: In a mouse bone marrow chromosomal aberration assay (MRID 41661302), 5 ICR mice/sex/dose were administered aldicarb technical [99.75% ai] in sterile deionized water at doses of 0.1, 0.2, and 0.4 mg/kg by oral gavage. Control mice (5/sex/dose) received either sterile deionized water (10 mg/kg) or cyclophosphamide (80 mg/kg). Bone marrow samples were taken 6, 18, and 30 hours after treatment from aldicarb treated mice, 18 hours after treatment in positive control mice, and 30 hours after treatment in negative control mice.

Mortality was observed in male and female mice at the 0.4 mg/kg dose, as well as signs of toxicity (dyspnea, tremors). The test article, aldicarb technical, failed to induce any significant increase in

the frequency, percentage, or specific type of structural chromosome aberration in bone marrow of treated mice in this study.

This study is classified as **Acceptable/Guideline** requirement (§84-2 (b)) for a structural chromosome aberration assay.

A.3.7 Neurotoxicity

870.6100 Delayed Neurotoxicity Study – Hen

EXECUTIVE SUMMARY: In a neurotoxicity study in hens (MRID 00080699), the LD_{50} (9.0 mg/kg), ½ of the LD_{50} (4.5 mg/kg), and ¼ of the LD_{50} (2.25 mg/kg) dosage of aldicarb (compound 21149) were administered to different groups of chickens.

A single peroral dose of 4.5 mg/kg or thirty daily peroral doses of 4.5 or 2.25 mg/kg of compound 21149 caused no delayed ataxia or apparent limb paralysis either during the dosage regimen or for thirty days following the last dose. In the highest levels given (9.0 mg/kg), four of the six birds died within two weeks of the beginning of peroral dosing but without showing any overt ataxia or limb paralysis. Based on observed symptomology, it would appear the compound 21149 produces only typical cholinergic symptoms and does not produce ataxia or those signs normally attributed to demyelination.

This study is classified as **Acceptable/Guideline** requirement for a delayed neurotoxicity study in the hen.

870.6200 Acute Neurotoxicity Screening Battery

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 43442301), 22 Sprague-Dawley rats/sex/group were administered aldicarb [99%] once *via* gavage at dose levels of 0, 0.05, 0.1, and 0.5 mg/kg, respectively. Functional Observational Battery (FOB) and a Motor Activity test (MA) were performed on 12 rats/sex/group prior to the study, at the time of peak effect (0.5 hour after dosing for FOB; 1 hour after dosing for MA), and on post-dose days 7 and 14. Blood (plasma, RBC, and whole blood) and whole brain cholinesterase measurements were made on 5 rats/sex/dose at the estimated time of peak effect (0.75 hour) and at 8 hours after dosing. On day 15, 6 rats/sex/dose were perfused and the high-dose and control groups were subjected to a neuropathological examination.

There were no treatment-related deaths or significant effects on body weight or food consumption, although both sexes at the high-dose level displayed a lower body-weight gain (81% of control) during the first week compared to the control. Ophthalmoscopic examination were comparable among the groups in both sexes. Clinical signs of cholinesterase inhibition were observed during the FOB at the high-dose level. At 0.5 hours post dose, the high-dose rats displayed tremors, lacrimation, salivation, decreased body temperature, increased respiration, decreased arousal, decreased activity and decreased reactivity, and decreased fore- and hind-limb grip strength. Automated motor activity was significantly decreased (74%-82%) at 1 hour post dose at the high-dose level. At the mid-dose level, only forelimb grip strength was significantly decreased at one hour post dose. (17%; $p<0.05$). No significant behavioral effects were observed on days 7 and 14 at any dose level.

Toxicologically-significant effects were observed on blood AChE activity in all dose groups at the peak-effect time (0.75 hour) after dosing, and there was recovery by 8 hours post dose. At the high-dose level, whole brain AChE activity (males 45%**, females 50%**) and all three blood measures of AChE activity were significantly decreased (whole blood 65%/76%**; plasma 92%/94%**; RBC 51%/54%**, male/female, respectively) at 0.75 hours post dose. At the mid-dose level, whole blood (male 61%**, female 54%**), plasma (male 86%, female 73%), and RBC (male 47%**, female 31%) AChEI was observed in both sexes, although statistical significance was not always attained. Brain AChEI was significantly decreased in females at 0.1 mg/kg (16%). At the low-dose level (0.05 mg/kg), whole blood (males 15%, females 29%) and plasma (males 34%, females 47%) AChEI was observed, although statistical significance was not attained due to the large variability in the data. However, comparison with the pre-dose values demonstrates that the inhibition (whole blood) is both statistically (females) and toxicologically (both sexes) significant.

No neuropathological changes were observed grossly or microscopically. At the high-dose level, females in the group that was perfused displayed brain weights that were statistically-significantly decreased compared to the control, but since no similar decrease was observed in the other female brain weights, the finding was not considered toxicologically significant.

The NOAEL is <0.05 mg/kg. The LOAEL is 0.05 mg/kg based on decreased whole blood and plasma AChEI. The NOAEL for brain AChEI is 0.05 mg/kg and the LOAEL for brain AChEI is 0.1 mg/kg.

This acute neurotoxicity study in the rat is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870. 6200; §81-7] for an acute neurotoxicity study in the rat.

NOTE: Previously, the Hazard Identification Assessment Review Committee (HIARC) did not consider the plasma AChEI observed at the 0.05 mg/kg dose level to be adversely/biologically significant, due to the large standard deviation and lack of statistical significance (TXR # 0050534, dated March 6, 2002). However, further analysis of the data from this study and the non-guideline acute neurotoxicity studies resulted in a determination that *the 0.05 mg/kg dose level is an effect level in this study. Based on the fact that the methodology used for AChEI determinations in this study may not be ideal for the assessment of a carbamate chemical due to reversibility, the actual magnitude of the inhibition in this study may have been greater. Although a large variability was noted in all of the AChEI data in this study, an examination of the individual AChEI data and a statistical analysis of the female whole blood data (performed by ORD)* ***resulted in a determination*** *that all dose levels are significantly different from the control.*

870.6200 Subchronic Neurotoxicity Screening Battery

EXECUTIVE SUMMARY: In this subchronic rat neurotoxicity study (MRID 43829602), three groups of Crl:CD® (SD) BR rats, consisting of 27 animals/sex/group, were gavaged with 0.05, 0.20, or 0.40 mg/kg/day of aldicarb [tech., 98.9%] for at least 13 weeks (MRID 43829602). A control group of 27 animals/sex was gavaged with the water vehicle. Twelve animals/sex/group were selected for FOB and MA testing, and 15 animals/sex/group were selected for serial AChE analyses. Six rats/sex/dose were anesthetized, perfused, and sacrificed for histopathology. Central nervous system (CNS) sections were embedded in paraffin, while peripheral nerves and spinal ganglia were embedded in plastic.

No treatment-related deaths occurred. One male each in the control, 0.20, and 0.40 mg/kg/day groups died during the last week of the study, on Day 53, and on Day 10, respectively. Tremors and salivation in the males and females occurred in the 0.20 and/or 0.40 mg/kg/day groups. Body weights were decreased in the males from the 0.40 mg/kg/day group, ranging from 7.2 to 9.2% during the 13 weeks, while the females did not have any statistically significant changes in body weight. Male body weight gains were decreased in the 0.40 mg/kg/day group ranging from 10.3 to 29.5% during the 13 weeks. The males from the 0.40 mg/kg/day group had decreased food consumption (6.9 to 16.9%) during Weeks 1, 2, 3 ,4, 8, and 9; and no changes were noted for the females. Food efficiency was decreased (5.8 to 15.4%) for the males in the 0.40 mg/kg/day group during the 13 weeks. Home cage and arena tremors (ranging in severity from slight to moderate) were increased in some males and females from 0.20 and 0.40 mg/kg/day groups during treatment regimen. The pupil size was pinpoint in some male and female rats from all dose groups during Weeks 4, 8, and 13, ranging in incidence from 16.7% to 100%. For the 0.40 mg/kg/day group, the tail pinch response was decreased in Week 8 for some females and for both males and females in Week 13. Hindlimb grip strength for males in the 0.40 mg/kg/day group was decreased ranging from 11.9 to 26.1%. Forelimb grip strength decreased (ranging from 8.3 to 24.8%) for the males and females in the 0.40 mg/kg/day group. The tail flick latency times for females in all doses groups for all testing periods were consistently increased ranging from 2.9 to 46.7%. Body temperature for females from the 0.40 mg/kg/day group on Weeks 4 and 13 was decreased by 1.6 and 1.8%,

respectively. Males and females from the 0.20 and 0.40 mg/kg/day groups had decreased total motor activity counts (ranging from 9.6 to 55.1%) on all occasions, except for males in the 0.20 mg/kg/day group during Week 4. The linear constructed variable (rate of linear change of activity counts) was different for both sexes from the 0.40 mg/kg/day group on all occasions and for males and females from the 0.20 mg/kg/day group on all occasions, except for females in the 0.20 mg/kg/day group at Week 8.

For males and females, at 0.2 and 0.4 mg/kg, plasma, whole blood and RBC AChEs were statistically significantly inhibited from weeks 4-13 and were roughly 90% for plasma, 50-70% for RBCs, and 62-87% for whole blood. At 0.05 mg/kg, whole blood (42-61%), RBCs (24-39%) were also significantly inhibited at weeks 4-13. Plasma AChEs were not statistically significantly inhibited for either sex, despite inhibitions of 61-78%. In general, the level of inhibition in the blood did not increase or decrease between weeks 4 and 13, though some increases were seen across time at the 0.05 mg/kg level. Similarly, whole brain AChEs (left hemisphere) were significantly inhibited for both sexes at all-time points after 0.2 mg/kg (26-46%) and 0.4 mg/kg (49-68%). At 0.05 mg/kg, only for females at week 13 was this measure significantly inhibited (12.8%). The level of brain inhibition at 0.2 mg/kg and 0.4 mg/kg, did show some increase across weeks 4-13, suggestive of some cumulative effect. Whole brain AChEI at 0.4 mg/kg, between weeks 4 and 13 went from 57.8-64.3% and from 56.7-68.4% in females. At 0.2 mg/kg, whole brain AChEI went from 25.7%-42.2% in males and 33.1-46.2% in females, from weeks 4-13. Among specific regions, cerebellum showed effects similar to whole brain, with significant inhibition only in females at week 13 (21%) at 0.05 mg/kg. Other regions were less sensitive, none showing significant effects at 0.05 mg/kg at any point, while almost all showed significant effects at 0.4 mg/kg. Frontal cortex and hippocampus showed similar patterns, with week's 8-13 showing significant decreases at 0.2 mg/kg and at all weeks at 0.4 mg/kg. Caudate/putamen was least sensitive, with significant changes only in females at weeks 8-13 at 0.4 mg/kg. Ophthalmoscopic examination and gross and histopathological evaluations did not reveal significant aldicarb-related changes. An increased incidence of slight axonal degeneration in the sciatic nerve, described as affecting only individual nerve fibers, were found in 3 high dose males, vs. one control rat, and 2 high dose females, vs. one control rat, but these lacked statistical significance.

The LOAEL is 0.05 mg/kg/day based on the FOB findings (pinpoint pupils) and AChE inhibition in blood and brain.

The NOAEL is <0.05 mg/kg/day.

This subchronic neurotoxicity study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.6200] for a subchronic oral neurotoxicity study in rats.

870.6300 Developmental Neurotoxicity Study

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 43829601) groups of 30 presumed pregnant Sprague-Dawley (Crl:CD7 BR VAF/Plus7) rats were administered Aldicarb [98.9%] by gavage at doses of 0, 0.05, 0.10, or 0.30 mg/kg/day on gestation day (GD) 6 through lactation day 10. The offspring were not administered the test material. Clinical observations, a

FOB, body weights, and reproductive data were recorded for the dams (F_0). Pups (F_1) were weighed, monitored for emergence of vaginal perforation or balanopreputial separation, observed until approximately postnatal day 65, and given neurobehavioral evaluations (FOB, motor activity, learning and memory test, auditory startle response). Plasma, RBC, and brain AChE activities were measured in both dams and pups. Neuropathological assessment of high dose and control pups were made on day 11 and day 65.

On treatment days, tremors were observed in as many as 11 and as few as 1 F_0 dams given 0.3 mg/kg. Clinical signs seen in the FOB on GD6 in 0.3 mg/kg/day dams, were tremor (10/10), lacrimation (7/10), salivation (6/10), stained fur (7/10), hunched posture (4/10), ataxia (9/10), lip smacking (4/10), decreased body temperature and miosis (10/10). The mean number of rears was also reduced (p # 0.05) in high dose dams (0.6) as compared to controls (7.9). During lactation, tremors or a few other signs were observed on days 0-2 in a few 0.3 mg/kg dams only. Clinical signs or changes in the FOB were not observed in any other dose group or the controls.

Mean maternal body weights of the 0.3 mg/kg/day group were significantly less (6%) than the controls beginning on GD 9 and continuing until GD20. Overall body weight gain during gestation was also significantly less in the 0.30 mg/kg/day dams (17%) in comparison to controls. During lactation, body weights of these dams were significantly ($p \leq 0.05$) less than controls only on day 4. Recovery was evident in high-dose dams after cessation of treatment with day 21 body weights 100% of the control value. No differences were seen between body weights or in body weight gains of the 0.05 or 0.10 mg/kg/day groups during gestation or lactation.

Mean maternal plasma AChE (ca 80%) and RBC AChE (27%) activities were significantly reduced in 0.3 mg/kg dams on GD 7 and lactation day 7 as compared to controls. On GD 7, plasma AChEI in 0.1 mg/kg dams was 40%, (not statistically significant), but much less later. No inhibition of AChE was seen in the brains of dams tested on lactation day 11 or in the plasma, RBC, or brain activity of the F_1 males or females tested on lactation days 4, 10, or 11. In many cases, less than 5 rats were used, limiting the power or sensitivity of these measures. No statistically significant effects were observed on duration of gestation, total number of pups delivered, pup survival indices, or percent male pups. There were no differences between treated and control groups in the emergence of balanopreputial separation or vaginal perforation.

A few treatment related effects on FOB measures and motor activity changes were observed in the 0.1 or 0.3 mg/kg pups during lactation and post-weaning. Motor activity was significantly decreased, about 30%, in both 0.1 and 0.3 mg/kg males on day 17. A 29% decrease was also seen in the 0.05 mg/kg group, but it did not reach statistical significance. No differences in motor activity were seen on days 13 and 21. There is normally, and, here in control animals, an increase in motor activity on day 17 in relation to either day 13 or day 21. Dosed males showed reduced or absent increases on day 17 in relation to days 13 or 21. At day 60, motor activity was significantly increased in the 0.1 mg/kg males for the whole session (20%) and 30% for the 10-20 minute interval. For the 0.3mg/kg males overall activity was not significantly different (14% increase) but for the 10- 20 minute interval a significant 34% increase was seen.

FOB observations were made on F_1 animals on postnatal days 14, 21, 35 and 63. On days 35 and 63 high-dose F_1 males made significantly fewer rears (and fecal boli) in the open field. Number of rears were also reduced in high-dose females at day 35. Decreased hindlimb grip strength (20%) and splay (15%) were also found in mid and high dose females on Day 35.

On day 63, high dose males had increased latency to first step (12/20 waiting 9 seconds vs. 3/20 controls); significantly reduced forelimb grip strength (20%); and an increased latency on the first trial (15 vs. 10 secs), but not the second trial or average latency, to a heat stimulus. No consistent effects attributable to treatment were seen on startle reflexes and no differences found on speed or errors in the learning and memory test. In summary, while many of these measures are isolated, there do appear to be a number of significant differences noted in high dose males at all-time points.

Pup body weights adjusted for litter size from high-dose dams were significantly lower than controls on lactation days 0 (8%), 4 (11-13%), and 7 (males and females), lactation day 11 (males), and lactation day 17 (females). Male and female pups from 0.1 mg/kg/day dams also had significantly lower body weights than controls on lactation days 7 and 17, 8% and 6%, respectively. Adjusted body weights from the mid- and high-dose dams were not significantly different by lactation day 21, where adjusted pup body weights were 95 and 93%, respectively, for males and 95 and 94%, respectively, for females of the corresponding control value. However, unadjusted mean body weights of these F_1 male and female rats earlier given 0.1 and 0.3 mg/kg/day were still depressed consistently throughout the post-weaning period. Significant differences occurred at weeks 0, 2, and 4 for the mid- and high-

dose males (6-8%; 10-15%) and high-dose females (13-7%), and at week 2 for the mid-dose females (4%). Body weight gain for 4 weeks after weaning was significantly less than controls for the mid- and high-dose males (ca 8%) but no differences in weight gains were seen in females.

Gross necropsies, brain weights and histological evaluations of the nervous system did not reveal aldicarb related effects. No significant treatment related changes in brain morphometric measurements on day 60 were noted.

Maternal toxicity at 0.30 mg/kg/day included clinical signs of toxicity such as tremor, salivation, and lacrimation, blood AChEI, and 17% reduced body weight gain during gestation.

The maternal LOAEL is 0.10 mg/kg/day based on plasma AChEI of 40% on GD 7. The maternal NOAEL is 0.05 mg/kg/day.

The offspring LOAEL is 0.10 mg/kg/day based on reduced body weights from birth through postweaning and on decreased motor activity on day 17 in male pups. The offspring NOAEL is 0.05 mg/kg/day.

This developmental neurotoxicity study in the rat is classified **Acceptable/Guideline**, and it satisfies the guideline requirement for a developmental neurotoxicity study [83-6; OPPTS 870.6300] in rats. Additional data on positive controls and morphometric data should be provided.

A.3.8 Metabolism

870.7485 Metabolism – Rat

In a metabolism study in rats (MRID 00102022 and 00102023), aldicarb was rapidly absorbed, widely distributed, and rapidly excreted, with more than 90% excreted in the urine within 24 hours after either acute or repeated oral doses. Aldicarb is rapidly metabolized to aldicarb sulfoxide, then slowly converted to aldicarb sulfone. The metabolism of aldicarb involves both hydrolysis of the carbamate ester and oxidation of the sulfur to sulfoxide and sulfone derivatives, which have been shown to be active cholinesterase inhibitors. Elimination of aldicarb and its metabolic products occurs primarily *via* the urine, with minor routes of excretion *via* the lungs as carbon dioxide.

This study is classified as **Acceptable/Guideline** requirement for a metabolism study in the rat.

870.7600 Dermal Absorption – Rat

No acceptable dermal absorption data are available for aldicarb.

A.3.9 Immunotoxicity

870.7800 Immunotoxicity

EXECUTIVE SUMMARY: In a repeat-dose immunotoxicity study (MRID 41054601), aldicarb was administered to female Swiss Webster mice or to female B6C3F1 mice in the drinking water at 0.1, 1.0, 10, 100, and 1000 ppb for 34 consecutive days. Parameters evaluated included splenic anti-sRBC plaque-forming cells, splenic lymphocyte blastogenic responses to mitogens, splenic lymphocyte response to allogenic lymphocytes, host resistance to influenza virus challenge, serum anti-sRBC hemagglutination titers, total and differential leukocyte counts, erythrocyte count, hemoglobin, hematocrit, body and organ (spleen, thymus, liver, brain) weights, gross/microscopic pathology of the immune system organs and tissues, and water and food consumption. Aldicarb did not significantly affect any of these parameters. Immunosuppressive responses in positive control (cyclophosphamide-treated) animal groups verified the sensitivity of the immune function assays. The stability of aldicarb under the experimental conditions of the study was verified by chemical analyses. It was concluded that aldicarb is not immunotoxic.

In another repeat-dose immunotoxicity study (MRID 00157981), aldicarb was administered to female $B_6C_3F_1$ mice *via* drinking water at dose levels between 1 ppb and 100 ppb for 34 days. No significant effect on numbers or percentage of splenic total T-lymphocytes, T-helper cells, T-suppressor/cytotoxic cells, or B-cells was observed. Additionally, aldicarb had no significant effect on either splenic natural killer cell function or cytotoxic T-cell function.

These studies are classified **Acceptable/Non-guideline**, and together they satisfy the guideline requirement for an immunotoxicity study (870.7800).

A.3.10 Special/Other Studies

Cholinesterase Inhibition Studies

EXECUTIVE SUMMARY – This series of non-guideline cholinesterase inhibition studies (MRID 47994302-47994305) was undertaken to evaluate any differences between postnatal day 11 (PND 11) pups and adult rats with regard to cholinesterase inhibition.

Dose Range-Finding Study (MRID 47994302): This study was performed to determine the dose levels for use in the time to peak effect study (MRID 47994304). Adult Crl:CD (SD) rats (0.1 or 0.3 mg/kg) and PND 11 pups (0.025, 0.05, or 0.1 mg/kg) were administered single doses of aldicarb in deionized water *via* gavage (6/sex/dose for both age groups). At 60 minutes post dose, cholinesterase activity was assessed in the RBC and brain compartments.

Results: Slight whole body tremors were observed in the adult rats at 0.3 mg/kg and in PND 11 pups at 0.1 mg/kg. A dose-related reduction in cholinesterase activity (both compartments) was observed at all dose levels in both sexes and age groups. The dose levels selected from this study for the time-to-peak-effect study were 0.08 mg/kg (adult rat) and

0.01 mg/kg (PND 11 pup). Following consultation with HED, a second dose level for the PND 11 pups of 0.02 mg/kg was included in the time-course study.

Comparative Dose-Study (MRID 47994303): This comparative study was to compare the amount of RBC or brain AChEI in adult or PND11 male Crl:CD (SD) rats after a single gavage dose. Aldicarb in deionized water was administered once *via* gavage (5 ml/kg) to 6 adult male and 6 PND11 male Crl:CD (SD) rats/sex/dose of 0, 0.01 or 0.04 mg/kg. Adult rats were euthanized approximately 40 minutes and juvenile rats at 60 minutes post-dosing, times that were considered to be the peak-effect times for each age group.

Results: There were no clinical findings at 20 minutes and 40 minutes (adult males) or 20 and 60 minutes (juvenile males) following dose administration. There were no changes in RBC and whole brain cholinesterase activity in adult males at either dose level. In PND 11 males, RBC cholinesterase activity in the 0.01 mg/kg and 0.04 mg/kg groups was 32% and 74% lower, respectively, compared to PND 11 control males at approximately 60 minutes post-dosing. Whole brain cholinesterase activity in PND 11 males was 36.7% lower at 0.04 mg/kg than control PND 11 males. There were no significant differences on mean brain weights in adult or PND 11 males at either dose level.

Time-Course Study (MRID 47994304): Aldicarb [99.8% ai; Lot #: 1218200307] in deionized water was administered once *via* gavage (5 mL/kg) to 6 adult and 6 PND 11 Crl:CD (SD) rats/sex/dose/sacrifice time at doses of 0 or 0.08 mg/kg (adult rats), and 0, 0.01 mg/kg, or 0.02 mg/kg (PND 11 pups) to determine the time of peak cholinesterase inhibition. RBC and brain cholinesterase activities were determined at 20, 40, 60, 120, 240, and 480 minutes after dosing in the adult (0.08 mg/kg) and PND 11 (0.01 mg/kg) groups (controls evaluated at 20 or 480 minutes). PND11 pups of the 0.02 mg/kg dose group were assessed at 40, 60, 120, and 240 minutes after dosing (controls evaluated at 60 minutes).

Results: All rats (both age groups) survived to scheduled sacrifice, and there were no clinical signs. Maximal RBC inhibition was observed at 20 minutes in adult females and at both 20 and 40 minutes in adult males. In the brain, maximal inhibition was observed at 40 minutes in both sexes of adult rats. In the PND 11 pups, maximal RBC inhibition was observed 60 minutes (males) and 40 minutes (females) at 0.10 mg/kg and at 60 minutes (both sexes) at 0.02 mg/kg. Brain inhibition was maximal at 40-60 minutes in the male PND 11 pups and at 60 minutes in the female PND 11 pups. Based on the results of this time-course study, times of 40 minutes and 60 minutes were selected as the time of cholinesterase determination in the definitive dose-response study for adults and PND 11 pups, respectively.

Dose-Response Study (MRID 47994305): In the definitive dose response study, aldicarb [99.8% ai; Lot #: 1218200307] was administered once *via* gavage to 8 adult Crl:CD (SD) rats/sex/dose at dose levels of 0, 0.03, 0.05, 0.065, 0.08, 0.15, or 0.3 mg/kg, and to 8 PND 11 pups/sex/dose at dose levels of 0, 0.005, 0.01, 0.02, 0.04, or 0.08 mg/kg. Erythrocyte and brain cholinesterase activities were determined ((Hunter et al., 1997 modification of the Ellman reaction (Ellman, et al., 1961))) at the estimated time of peak-effect of 40 minutes post-dosing in adult rats and at 60 minutes post-dosing in PND 11 pups. Samples were

maintained in an ice-water bath from point of collection until analysis for cholinesterase activity. Samples were analyzed within one hour of sample collection.

Results: *Clinical signs.* There were no treatment-related effects on mortality in either age group. All 0.3 mg/kg adult rats (both sexes) showed slight to moderate tremors of the limbs by 20 minutes post-dosing and at sacrifice at 40 minutes, and 3 adult males and 4 adult females in the 0.15 mg/kg group displayed slight tremors at 40 minutes. No tremors were observed in the PND 11 pups at any dose level, and none of the adult rats displayed tremors at 0.08 mg/kg, which was the only common dose level between the age groups and highest dose level in the PND 11 pups.

RBC Cholinesterase. PND 11 pups were more sensitive than the adult rats, based on a comparison of RBC cholinesterase inhibition. There was a dose-related decrease in RBC cholinesterase activity in the adult rats (both sexes), with the magnitude of the reduction (28%) at the lowest dose (0.03 mg/kg) in the females being biologically significant. An assessment of the adult sexes combined at 0.03 mg/kg showed 20% inhibition, which was statistically significant. At the two highest dose levels, nearly complete inhibition of RBC cholinesterase activity was observed in both sexes of adult rats (96%-99% at 0.15 mg/kg and 94%-97% at 0.3 mg/kg). The magnitude of the AChE activity at these two highest doses corresponds with the tremors that were observed in adults at either 20 or 40 minutes post-dosing. In the PND 11 pups, both sexes displayed a dose-related reduction in RBC cholinesterase activity, with the magnitude of the response being 28%-34% at 0.01 mg/kg and 85%-87% at the highest dose tested (0.08 mg/kg). At 0.005 mg/kg (lowest dose tested), ~10% RBC cholinesterase inhibition was observed in the PND 11 pups.

Brain Cholinesterase. PND 11 pups were more sensitive than the adult rats, based on a comparison of brain cholinesterase inhibition. In the adult rat, a statistically significant reduction (dose-related) in brain cholinesterase activity was observed at dose levels of 0.05 mg/kg and above in both sexes. The magnitude of the decrease was 6%-9% at 0.05 mg/kg, 9%-10% at 0.065 mg/kg, 13%-18% at 0.08 mg/kg, 27%-28% at 0.15 mg/kg, and 43%-50% at 0.3 mg/kg. Brain cholinesterase activity was decreased at all doses except at the lowest dose (0.005 mg/kg) in the PND 11 pups (both sexes). The magnitude of the decrease was 8% at 0.01 mg/kg, 15%-16% at 0.02 mg/kg, 38%-44% at 0.04, and 59%-60% at 0.08 mg/kg in the PND11 pups (both sexes). Generally, pups were 4-8 fold more sensitive than the adult rats, depending on the sex and dose evaluated.

A benchmark dose analysis of the cholinesterase data (RBC and brain) was performed that provides both the BMD_{10} and $BMDL_{10}$ of adults and PND11 pups (B. Sarkar, 7/1/2010, D379831).

A separate benchmark dose analysis of the definitive dose-response data demonstrated the following BMD_{10}s and $BMDL_{10}$s for adult cholinesterase:

	RBC BMD_{10}	RBC $BMDL_{10}$	Brain BMD_{10}	Brain $BMDL_{10}$
Adult females	0.0242 mg/kg	0.0144 mg/kg	0.0615 mg/kg	0.0498 mg/kg
Adult males	0.0228 mg/kg	0.0153 mg/kg.	0.0535 mg/kg	0.0484 mg/kg

A separate benchmark dose analysis of the definitive dose-response data demonstrated the following BMD_{10}s and $BMDL_{10}$s for PND 11 pup cholinesterase:

	RBC BMD_{10}	RBC $BMDL_{10}$	Brain BMD_{10}	Brain $BMDL_{10}$
PND11 females	0.00731 mg/kg	0.00387 mg/kg	0.0136 mg/kg	0.0103 mg/kg
PND11 males	0.00477 mg/kg	0.00294 mg/kg	0.0143 mg/kg	0.0112 mg/kg

A ratio of the BMD_{10} adults to BMD_{10} PND11 pups provides a data derived FQPA factor.

RBC FQPA (female)
Adult BMD_{10}/PND 11 BMD_{10} = 3.31

Brain FQPA (female)
Adult BMD_{10}/PND 11 BMD_{10} = 4.52

RBC FQPA (male)
Adult BMD_{10}/PND 11 BMD_{10} = 4.78

Brain FQPA (male)
Adult BMD_{10}/PND 11 BMD_{10} = 3.74

These studies are classified as **Acceptable/Non-guideline**. These studies do not satisfy a guideline requirement for aldicarb. They satisfy the generic data call-in requirement for aldicarb for a comparative cholinesterase study in adult rats versus PND 11 pups.

Special Acute neurotoxicity study

EXECUTIVE SUMMARY: Two special (non-guideline) acute neurotoxicity studies (MRIDs 45068601 and 45150701) were performed using groups of Long-Evans Crl:(LE)BR rats of varying ages to assess differences in survival, behavior, and AChE levels in whole blood and brain following single acute oral doses of aldicarb.

In the **original** study (MRID 45068601), groups of 2-3, then 5-10 PND 17 pups, PND 27 rats, and >PND 67 (adult) rats were administered acute oral doses between 0.05 mg/kg and 0.35 mg/kg of aldicarb [>99%] in corn oil *via* gavage, and the highest dose that produced clear signs of cholinergic toxicity without death or considerable weight loss was determined (called a maximum tolerated dose (MTD)) for each age group. For the full study, PND 17 rat doses were 0, 0.05, 0.1, or 0.18 mg/kg, PND 27 rat doses were 0, 0.08, 0.15, and 0.26 mg/kg, and PND >67 (adult) rat doses were 0, 0.1, 0.2, and 0.35 mg/kg. Ten rats/sex/dose were examined by a FOB and a MA prior to the study, at the time of peak effect, 1 hour after dosing for the FOB and immediately after the FOB for MA; and on post-dosing days 1, 3, and 7. Blood (whole blood; trunk blood) and whole brain cholinesterase determinations (by the radiometric method) were made on 4 rats/sex/dose at 1 hour after dosing (all groups and dose levels) and at 24 and 72 hours after dosing for the highest dose level in each age group.

In the **replication** study (MRID 45150701), groups of 4 (cholinesterase assessment) and 8 (lethality) PND 17 pups and PND 66-72 adults were administered acute oral doses of aldicarb [98%] in corn oil *via* gavage at dose levels of 0, 0.05, 0.1, 0.2, and 0.3 mg/kg (AChE activity (whole blood and brain) at 1 hour post dose) and dose levels between 0.15 and 0.4 mg/kg (lethality assessment).

In the original study, at a comparable dose level of 0.3 mg/kg, 50% of the PND 17 pups died (5/8 males, 3/8 females; 8/16 total), 9% of the PND 27 rats died (1/11 males, 1/11 females;

2/22 total), and there were no adult deaths at this dose level, indicating the younger animals were more sensitive to this acute dose. The MTDs for each age group were: 0.18 mg/kg for PND 17 rats; 0.26 mg/kg for PND 27 rats; and 0.35 mg/kg for adult rats. PND 17 rats showed only a few behavioral effects at their MTD (tremors, gait changes/ ataxia, and a slight effect on the righting response). PND 27 and adult rats showed many significant behavioral responses at doses lower than their MTD (0.1 mg/kg (adults) or 0.15 mg/kg (PND 27)), as well as at their MTD. The LOAEL for PND 27 pups was 0.08 mg/kg, where a significant decrease in the tail pinch response was seen in males. For adults, at 0.1 mg/kg, there were significant effects on tremors, miosis, and decreased motor activity in both sexes, gait changes/ataxia and decreased arousal in females. In the automated motor activity assessment, aldicarb produced dose-related decreases in PND 27 and adult rats (5-80%), but no decrease in motor activity was observed in PND 17 rats.

Statistically-significant whole blood AChEI was observed at all dose levels in all age groups, and significant brain AChEI was observed at all dose levels in all age groups, although the PND 17 female pups and high-dose adult rat values did not attain statistical significance. For brain AChEs, there was significantly more inhibition for PND 17 rats than adults based on their ED_{50} values (0.12 mg/kg vs. 0.29 mg/kg, males; 0.15 mg/kg vs. 0.28 mg/kg, females). There were no significant differences found in levels of blood AChE among the 3 age groups. At 0.05 mg/kg in PND 17 rats (lowest dose tested), blood inhibition was 67%-75% and brain inhibition was 15%-30%. At 0.08 mg/kg in PND 27 rats (lowest dose tested), blood AChE inhibition was 85% and brain AChE inhibition was 20%-25%. At 0.1 mg/kg in the adult rats (lowest dose tested), blood AChE inhibition was 85% and brain AChE inhibition was 10%.

In the replication study, there were no deaths at either age group below 0.4 mg/kg, which is in sharp contrast to the findings in the original study. With respect to AChE activity, the findings in the original study were repeated here. At the lowest dose tested (0.05 mg/kg), whole blood AChEI was 75% (males)/81% (females) in the PND 17 pups and 84% (males)/85% (females) in the adult rats. A dose-related increase in whole blood AChEI was observed at the three higher dose levels in both age groups, and at the highest dose tested (0.3 mg/kg), whole blood AChEI was 95% (males)/94% (females) in the PND 17 pups and 97% (males)/96% (females) in the adult rats. Brain AChEI was observed at all dose levels in both age groups, with the PND 17 pups displaying a greater (~2-fold) inhibition than the adults at the lowest dose tested (0.05 mg/kg). At (0.05 mg/kg), brain AChEI was 28% (males)/24% (females) in the PND 17 pups and 12% (males)/10% (females) in the adult rats. A dose-related increase in brain AChEI was observed at the three higher dose levels in both age groups, and at the highest dose tested (0.3 mg/kg), brain AChEI was 84% (males)/76% (females) in the PND 17 pups and 51% (males)/54% (females) in the adult rats.

The LOAEL is 0.05 mg/kg based on brain and whole blood AChEI in both sexes and all age groups. A NOAEL was not determined. PND 17 pups were more sensitive than the older rats with respect to brain AChEI, as evidenced by the greater magnitude of the inhibition of brain AChE activity at all dose levels compared to the older rats. Adult rats displayed a greater response with respect to the behavioral effects and motor

activity. Whole blood AChE activity was significantly inhibited (>75%) at all dose levels and age groups (except PND 17 males (67%) in original study).

This study is classified **Acceptable/Non-guideline**. It does not satisfy any guideline data requirement.

Human Oral Study

EXECUTIVE SUMMARY: In a double-blind, placebo-controlled acute oral human exposure study (MRID 42373001), which included 38 men and 9 women, with 6 men and 5 woman receiving both a dose and a placebo exposure, men were exposed to doses of 0, 0.01, 0.025, 0.05, 0.06, or 0.075 mg/kg of aldicarb, while women received 0, 0.025, or 0.05 mg/kg in orange juice with breakfast to be consumed over 15-30 minutes. A number of biological parameters were monitored before dosing, hourly for the first 6 hours after dosing, and at 24 hours after dosing. These measures included signs and symptoms (e.g., sweating), pulse and blood pressure, pulmonary functions (FEV-1 and FVC), saliva and urine output, pupil diameter, and plasma and RBC AChE activity.

The major endpoints seen in the study and discussed as potentially treatment-related were effects on RBC and plasma cholinesterase, sweating, light-headedness, headaches, salivation, and supine diastolic blood pressure. Aldicarb treatment of both males and females resulted in statistically significant inhibition of both RBC and plasma cholinesterases at all dose levels. Mean plasma and RBC cholinesterase inhibition 1 hour after dosing showed a dose-response for both sexes. Although the effect in men at 0.01 mg/kg was statistically significant, the RBC cholinesterase inhibition of 3.8% was not considered toxicologically significant. Peak effects were noted at 1 hour after the dose, and the degree and duration of effect increased with increasing dose. The magnitude of the RBC cholinesterase inhibition in males was 3.8%, 12%, 29%, and 38% with increasing dose, while the magnitude in the female was 20% and 36%.

One male in the 0.075 mg/kg group, who mistakenly received 0.06 mg/kg, developed diffuse and profuse sweating that came on within 2 hours and abated within 6 hours of dosing. Two other treated men, one given 0.05 mg/kg and another given 0.025 mg/kg, developed localized and mild sweating with onset within 2 hours of dosing, which also abated within 6 hours of dosing. One male given 0.075 mg/kg reported that he was lightheaded within one hour of dosing. Three men in the 0.01 mg/kg group reported headaches, two with onset within 6 hours of dosing and one within 8 hours. This long time of onset is beyond the peak of cholinesterase inhibition and the other effects seen here and in both Union Carbide study and the poisoning episodes.

None of the females developed any clinical signs or symptoms consistent with cholinesterase inhibition or treatment. Females given 0.05 mg/kg showed higher saliva output than controls, with marginal statistical significance. Observed changes in blood pressure were generally small in magnitude, limited to supine diastolic pressure, and statistically significant in some, but not other analyses. There were no treatment-related changes in standing or supine pulse, pupil size, or urine volume in either males or females. As expected, there were

no changes in hematology and clinical chemistry parameters. There were statistically significant increases in FVC in men at 0.010 mg/kg and 0.075 mg/kg dose, but these were not concluded to be treatment-related, based upon one way analysis of variance, which was not statistically significant and upon the observation that the statistically significant findings were likely a result of a drop in control values during the session.

The LOAEL = 0.025 mg/kg based on sweating seen in men and RBC cholinesterase inhibition. The NOAEL = 0.01 mg/kg.

This study is classified as **Acceptable/Non-Guideline**. There are no guideline requirements for human studies. The study is considered acceptable for evaluating potential effects from acute exposure to aldicarb. The Human Studies Review Board reviewed this study and concluded that the study is scientifically valid and the data are reliable and that the use of the human study endpoint was appropriate for human health risk assessment. The final report of the HSRB is available on the Agency website[17].

Appendix B. Physical/Chemical Properties

Table B.1. Physicochemical Properties of Technical Grade Aldicarb

Parameter	Value	Reference
Molecular Weight	190.3 g/mol	S. Mathur, 12/9/11, DP# 392450 [MRID 485225-04]
Physical State	Solid	
Melting range	96 - 97 °C	
pH	6.0	
Density	0.565 g/mL	
Water solubility	5191 mg/L at 20 °C	
Vapor pressure	0.9 mPa (25 °C)	
Octanol/water partition coefficient, Log (K_{OW})	1.06	
UV/visible absorption spectrum	UV absorption was conducted under acidic (λ = 772, 779, 757 nm), neutral (λ = 488. 757, 765 nm) and basic (λ = 765, 779, 757 nm) conditions.	

[17] HSRB Report: http://archive.epa.gov/hsrb/web/pdf/april2006mtgfinalreport62606-2.pdf

Appendix C. International Residue Limits

Table C. Summary of US and International Tolerances and Maximum Residue Limits for Aldicarb (098301)				
***Residue Definition*:**				
US		**Canada**	**Mexico[2]**	**Codex**
40 CFR 180.269 Aldicarb (2-methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl) oxime) and its cholinesterase-inhibiting metabolites 2-methyl-2-(methylsulfinyl) propionaldehyde O-(methylcarbamoyl) oxime and 2-methyl-2-(methylsulfonyl) propionaldehyde O-(methylcarbamoyl) oxime		2-methyl-2-(methylthio)propanal O-[(methylamino)carbonyl]oxime, including the metabolites aldicarb sulfoxide and aldicarb sulfone		Plant commodities: Sum of aldicarb, aldicarb sulphoxide and aldicarb sulphone, expressed as aldicarb.
Commodity[1]	***Tolerance (ppm) /Maximum Residue Limit (mg/kg)***			
	US	**Canada**	**Mexico[2]**	**Codex**
Bean, dry, seed	0.1			0.1 beans, dry
Beets, sugar, roots	0.05			0.05 (*) sugar beets
Beets, sugar, tops	1			
Citrus, dried pulp	0.6			0.2 citrus fruits
Coffee, bean, green	0.1			0.1 coffee beans
Cotton, undelinted seed[3]	0.2			0.1 cotton seed 0.01 cotton seed, oil, edible (*)
Cotton, gin byproducts[3]	0.4			
Grapefruit	0.3			0.2 citrus fruits
Lemon	0.3			
Lime	0.3			
Orange, sweet	0.3			
Peanut	0.05			0.02 0.01 peanut oil, edible (*)
Pecan	0.5			1
Potato	1	0.5		
Sorghum, grain, bran	0.5			
Sorghum, grain, grain	0.2			0.1
Sorghum, grain, stover	0.5			0.5 sorghum straw and fodder, dry
Soybean	0.02			0.02 soya bean, dry (*)
Sugarcane, cane	0.02			0.1
Sweet potato, roots	0.1			0.1 sweet potato
MRLs with NO US equivalent				
Barley				0.02
Barley straw and fodder, dry				0.05
Brussels sprouts				0.1
Grapes				0.2
Maize				0.05
Maize fodder (dry)				0.5

Table C. Summary of US and International Tolerances and Maximum Residue Limits for Aldicarb (098301)				
***Residue Definition*:**				
US		**Canada**	**Mexico[2]**	**Codex**
Meat (from mammals other than marine mammals)				0.01 (*)
Milks				0.01 (*)
Onion, bulb				0.1
Spices, fruits and berries				0.07
Spices, roots and rhizomes				0.02
Sunflower seed				0.05 (*)
Wheat				0.02
Wheat straw and fodder, dry				0.05
Completed: M. Negussie; 12/07/15				

[1] Includes all registered commodities and their established tolerances.
[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.
[3] Based on OECD tolerance calculation procedures using 2009 cotton field trial data.
*No residues expected

Appendix D. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1), the Agricultural Handler Exposure Task Force (AHETF) database. These data are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies that review may have included review by the Human Studies Review Board. Descriptions of data sources as well as guidance on their use can be found at http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html.

The Human Studies Review Board reviewed the aldicarb human study and concluded that the study is scientifically valid and the data are reliable and that the use of the human study endpoint was appropriate for human health risk assessment. The final report of the HSRB is available on the Agency website[18].

[18] HSRB Report: http://archive.epa.gov/hsrb/web/pdf/april2006mtgfinalreport62606-2.pdf

Appendix E. Commodity Specific Analysis for Aldicarb

Table E.1. Aldicarb PDP Monitoring Data Used for the Commodity Specific Analysis.	
Source of Data Used For Refinement	Maximum Residue (ppm)
Potato PDP Data (Import)	0.03796
Sweet Potato PDP Data (Domestic Plus Import)	0.07784
Sweet Potato Baby Food PDP Data (Domestic and Import)	0.0083

Table E.2. Commodity Specific Analysis for Aldicarb

Commodity (Food)	Age Group			Source		Exposure %aPAD		
	Amount Consumed (g)			Anticipated Residue (ppm)		Using FTD or PDP Data		
	Infant (10 kg)	*Pre-schooler (15 kg)*	*Females 13to49 (60 kg)*	*Monitoring (PDP)*	*Residue Threshold*[1]	*Infant*	*Pre-schooler*	*Adult-Female*
Potato	71	142	142	0.0380	0.029	100	**133**	33
Sweet Potato	78	156	156	0.0778	0.026		**300**	75
Sweet Potato (bf)	78	156	156	0.0083	0.026	24		

bf = baby food

[1] Residue Threshold = aPAD / Consumption = 0.00027 mg/kg-bw/day / [Amount Consumed (kg/day) / Body Weight (kg)]. The residue threshold (i.e. residue level that would result in risk at the level of concern) presented in this table is based on preschoolers, the subgroup with highest exposure.